FEATURE
Physician stress in the context of medical aid in dying

COMMENTARY
The resurrection of psychedelic psychiatry and its role in addiction treatment

ACADEMIC RESEARCH
The role of BDNF in Huntington Disease: A targeted analysis of 12 microarray studies

RESEARCH LETTER
The lasting effects of childhood trauma on mental health in adulthood

Mental Health
Constantly, our paths change and our minds remain malleable. We do our best to piece together the colourful fragments that are our lives. Sometimes parts of the puzzle overwhelm us; we focus on repairing these parts and unknowingly, other aspects start to crumble. We grasp onto the remaining pieces of organized puzzle-fighting for a chance to regain the control we once had. Thankfully, family, friends, and our own resilience help us get back on track and keep up with the ever-changing dynamics of life.

Modern medicine has been playing an increasingly large role in helping those who are struggling with mental illness. In this issue, we discuss the psychosocial and medical aspects of mental health, to raise awareness and reduce stigma around mental health-related illnesses.

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## Contents

**VOLUME 8 ISSUE 1 | SEPTEMBER 2016**

### EDITORIAL

3  Mental health in 2016: Current events and clinically actionable insights from neuroscience  
Mansoor Y., Squair J.W.

5  In memoriam: Laura Taylor  
McMillan J.

### FEATURE

6  When learning about the brain gets personal  
Krebs C., Beasley C.

7  Physician stress in the context of medical aid in dying  
Siden H.

9  Models and mechanisms in neurodegeneration: Towards neuroprotective therapy in Huntington disease  
Raymond L. A.

12  Mental illness and significant cognitive impairment among socially marginalized adults in Vancouver’s Downtown Eastside  
Jones A. A., Willi T. S., Honer W. G.

### REVIEWS

14  The association between female-factor infertility and depression and anxiety  
Rockwood N.M., Pendergast A.

### ACADEMIC RESEARCH

17  The role of BDNF in Huntington Disease: A targeted analysis of 12 microarray studies  
Xie R., Yang S., Ma F., Zhao E.Y.

23  Temporal changes in age at onset of multiple sclerosis: Importance of controlling for equal observation time  

27  Credible, centralized, safe, and stigma-free: What youth with bipolar disorder want when seeking health information online  
Noack K., Balram Elliott N., Canas E., Lane K., Paquette A., Lavigne J. M., Bipolar Youth Action Group, Michalak E. E.

### CASE AND ELECTIVE REPORTS

32  Resolution of acquired von Willebrand Syndrome secondary to hypertrophic obstructive cardiomyopathy following septal myectomy  
Hoggarth J., Rakowski H., Yeo, E., Ralph-Edwards A.

34  Could anticoagulation with Rivaroxaban have precipitated a spinal epidural hematoma: From independent mobility to paraplegia  
Sarwal G., Dandurand C., Lee A. Y., Vu V. H.

### COMMENTARIES

38  The resurrection of psychedelic psychiatry and its role in addiction treatment  
Skocylas R.

40  Tackling social isolation and loneliness through community exercise programs for seniors  
Hwang J., Wang L., Jones C.

42  I would tell you if I could: Language loss, depression, and the challenge of treating patients with aphasia  
Morrison M.

### NEWS AND LETTERS

44  Concussion and mental health: A concise review  
Ip A. H.

46  The lasting effects of childhood trauma on mental health in adulthood: Current knowledge and practical next steps for clinical practice  
Lake S.

48  Burnout and mental illness among Canadian physicians  
Rheume, A.
Mental health in 2016: Current events and clinically-actionable insights from neuroscience

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“Mental health” is an essential component of holistic health and well-being, and is defined by the World Health Organization as “a state of well-being in which every individual realizes his or her own potential, can cope with the normal stresses of life, can work productively and fruitfully, and is able to make a contribution to her or his community.” In the absence of mental health, “mental illness” refers to diagnosable disorders in which “alterations in thinking, mood, or behaviour (or some combination thereof) [are] associated with significant distress and impaired functioning.” The most common forms of mental illness include depression, anxiety, dementia, and schizophrenia. Mental illness can range in nature from subclinical to severe, and in length from single episodes to chronic disorders. It is important to note that the definition of being mentally healthy does not limit itself to the absence of mental disorders or disabilities. In addition, the definition of mental health varies across cultures and personal, subjective assessments. The effective promotion of mental health in society is essential in order to mitigate mental illness, and to improve quality of life among those living with a mental illness as well as those without.

It has been well-established that mental illness, like many other forms of disease, arises from a complex interaction of biological, psychological, and social factors. Unlike other diseases, however, classical imaging and blood tests have limited utility in the detection of mental illnesses. It is no surprise, then, that the complexity of the etiology and presentation of mental illnesses has brought about challenges in diagnosing, treating, and preventing mental illness. However, exciting advances in genetics, neuroimaging, and neurophysiology in the past decade have greatly impacted our ability to investigate and treat these disorders. Specific genes for disorders such as schizophrenia and post–traumatic stress disorder are being uncovered, neural circuits for depression are being identified, and neurotransmitter systems implicated in addictions, such as the dopaminergic system, are being analyzed with greater sophistication. Paired with an increasing understanding of the social determinants of health and their roles in precipitating mental illness, we are slowly working toward becoming more knowledgeable about and being better equipped to prevent and treat these disorders.

Mental health has also gained considerable attention in recent years in Canada. In 2006, a review by the Standing Senate Committee on Social Affairs, Science, and Technology identified that mental health needs of the incoming Syrian population will be of major concern.

In addition to the ongoing Syrian crisis, in February of 2016 the Supreme Court of Canada decriminalized medical assistance in dying (MAID) for “grievous and irremediable medical conditions.” The Supreme Court’s decision was made in the Carter v. Canada ruling (MAID) for “grievous and irremediable medical conditions.” The Supreme Court’s decision was made in the Carter v. Canada ruling (MAID) for “grievous and irremediable medical conditions.” Since then, the legislation governing MAID has been carefully articulated by decision–makers. The implementation of this new legislation will have a broad array of implications on healthcare providers, patients, and families alike. In the context of healthcare, the impact of MAID from the caregiver perspective has received relatively little attention. Furthermore, in states and countries where MAID has been approved, there is little evidence on the impact these life and death decisions have on physicians.

In this issue of the University of British Columbia Medical Journal (UBCMJ), we explore the arising complexities of mental health issues; Jordan W . Squair, MSc
on various forefronts. Dr. Lynn Raymond highlights exciting advances in the bridge between psychiatry and neurology, and how an increased understanding of underlying physiological mechanisms is leading to improved outcomes in neuro–psychiatric disorders. Furthermore, we are pleased to have Dr. Hal Siden discuss some of the issues around one of the most hotly contested topics in medicine: MAID. As medical director of Canuck Place Children’s Hospice, Dr. Siden provides unique insight into this topic and discusses the potential implications of this recent legislation on pediatric palliative care. In addition to these critically important topics, recent evidence suggests medical students are at an increased risk of developing mental health issues. On the other hand, medical students are positioning themselves as physicians to be abundantly exposed to patients suffering from a wide variety of mental health concerns. A feature article by Dr. Claudia Krebs and Dr. Claire Beasley includes an important discussion on the role medical education plays in raising awareness of mental health among medical students. Lastly, Andrea Jones, Taylor Willi, and Dr. William Honer present a discussion of mental health in the Downtown Eastside of Vancouver, providing insight into the most recent advances to understanding some of the social determinants of mental health. We hope that this latest issue of the UBCMJ sheds light on the complexities of mental illness and engages the readership on such a significant topic in our society.

References

In memoriam: Laura Taylor

I am deeply saddened to write about the loss of one of our community, Laura Taylor, a third year medical student at the Vancouver Fraser Medical Program. I knew Laura well and saw her passion for medicine, her intelligence, her fierce determination, and her persistent advocacy. She blazed a trail of change around meeting competencies while protecting her health. Our heartfelt condolences go out to her family, friends, colleagues, and hockey teammates.

Laura was drawn to follow in the medical footsteps of her grandfather, father, and older sister. The challenges of medical school were a perfect match for her brilliant mind and her caring heart. For more than half her life, Laura valiantly tried to overcome her long battle with the effects of depression, within the disease of bipolar disorder, but sadly the struggle finally took its toll. The family truly appreciates the compassionate care provided by numerous physicians over the years in Saskatoon, Prince George, Kelowna, and Vancouver.

Her legacy to us at the University of British Columbia (UBC) will be four-fold: accommodations considerations, research, stigma–reduction content in the curriculum, and a memorial fund.

Laura advocated for and developed accommodations with UBC Access & Diversity that would protect her health while allowing her to fulfill the competencies of the MD Undergraduate Program. This was groundbreaking for the UBC Faculty of Medicine and has set a framework for those who follow.

Part of her quest for betterment, both for her own situation and illness and for that of others dealing with mental illness, was to engage in research about mental illnesses. She was happy and proud to work with Dr. Todd Woodward in the Cognitive Neuroscience of Schizophrenia Lab, Department of Psychiatry, on research about schizophrenia and bipolar disorder.

Laura felt the burden of stigma associated with mental illness. She wanted to address and eliminate this stigma, but did not know how to tackle it herself. In her memory, her family is coordinating a country–wide campaign for stigma reduction. Her sister, Heather, will be working closely with us to include appropriate, evidence–based practices into our discussions with medical learners.

The UBC Faculty of Medicine, together with her family, has established a memorial fund in Laura’s name with the goal of raising funds to address stigma issues associated with mental illness and to support other related mental health initiatives within the MD Undergraduate Program. For more information or to give in memory, please visit http://memorial.supporting.ubc.ca/laura-taylor/. Donations can also be made to the Canadian Mental Health Association, either nationally or locally: www.cmha.ca and www.cmha.ca/branch_locations/kelowna-branch/.

It is hard not to wonder and worry about the stresses and pressures of medical school, residency, and practice, and to consider how they might have impacted Laura and might impact each of us. It is all of our responsibilities to monitor and look after ourselves and each other, not only in the legal jurisdiction of fitness–to–practice, but also in the more day–to–day maintenance of well–being and resilience. We will be thinking about ways to do this systemically within the Faculty of Medicine. Please think about ways to do this personally. You can contact your Student Affairs Assistant Dean or me directly with questions, ideas, comments, and concerns.

I appreciate the opportunity afforded to me by the University of British Columbia Medical Journal editors to write about Laura for this mental health focused issue. I have quoted extensively from the obituary written by her mother and thank her family for allowing me to do so. Please visit the memorial website to leave messages for her family.

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When learning about the brain gets personal

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When students learn about their patients, they strive to understand where illness originates, how it manifests throughout body systems, and how to develop a therapeutic approach. Over the course of their education, students develop clinical reasoning strategies to approach various illnesses.1 Psychiatric disorders are often particularly challenging as there is significant heterogeneity in symptomatology and course,2,3 and treatment is typically complex.4,5 Furthermore, while current thinking posits that psychiatric disorders result from dysfunction of brain circuits,6 the precise etiology and pathophysiology is not yet fully understood.6,9 This is in contrast to neurological disorders in which focal lesions are typically present. A lack of knowledge regarding mental illness may lead to misconceptions: that mentally ill individuals are dangerous, violent, or lazy, that they are responsible for their own illness, or that psychiatric disorders are not amenable to treatment. Misconceptions likely contribute to the stigma associated with these disorders,10 and consequently create barriers to accessing healthcare.11

Many facets need to be explored when approaching a curricular framework on psychiatric disorders. Despite the challenges of dealing with complex non–linear networks and the limitations of our current understanding, students need to receive up–to–date knowledge regarding the neuroscience underpinning these disorders. They also need to consider the impact of psychiatric disorders on the lives of patients. Over the years, we have developed an integrated approach to teaching about psychiatric disorders within the Brain and Behaviour block of the University of British Columbia MD undergraduate program, and more recently, within the renewed MD curriculum.12 Our aim is to provide students with a foundational knowledge base designed to facilitate parallel clinical experiences. Week–long case–based learning (CBL) cases bring to life a patient’s experience with mental illness. CBL sessions allow inquiry and clinical reasoning to be practiced in small group settings and provide a venue for discussion of relevant issues, such as biopsychosocial factors and a holistic approach to patient care. Lectures accompany the cases, helping students to focus their understanding of the major psychiatric disorders, underlying biological processes, and treatment options. In addition, large group discussion sessions provide an opportunity to consider the broader impact of mental illness on society. Neuroanatomy labs complement learning by emphasizing current understanding about how the brain creates emotions and behaviours. The approach to the neuroanatomy labs is that of a flipped classroom, where didactic knowledge is acquired before the session, and in–class time is used to apply knowledge to clinical cases. This approach has been shown to facilitate better integration and retention of content.13 Finally, we are extremely fortunate to have people with lived experience of mental illness come into the classroom to talk about how their lives have been impacted. This is a powerful teaching tool. We learn through their experiences and stories; when a patient talks about the distress that illness has caused by akathisia resulting from an antipsychotic medication, questions surrounding the mechanism of action of psychotropic medications and their side effects become more immediate and real.

Learning about neuroanatomical pathways—how these interact to define our mental state and how disruptions in these networks lead to psychiatric disorders—is interesting and also personal. Every time we learn about the anatomy of our bodies, we learn about ourselves, as well as our patients.14 When we learn about the anatomy of the brain, we learn how neural connections define our behaviour, our personality, and our humanity. When we look at the networks that define our behavioural output, we see our own patterns—we understand how the act of pushing the snooze button three times every morning is actually defined by neural connections.15 When we learn about the neurobiology of stress, we ourselves may be experiencing stress. When we learn about the neurobiology of mood and anxiety disorders, we may be feeling sad or anxious. In this way, we can appreciate how psychiatric disorders represent one end of a spectrum of behaviours we exhibit ourselves.

While psychiatric disorders represent one end of a spectrum of everyday emotions and behaviours, it needs to be recognized that these disorders are highly prevalent: almost everyone knows someone who is dealing with a mental health issue. In any given year, one in five Canadians will experience a mental health or addiction problem.16 Health care professionals are not immune. Suicide is considered an occupational hazard for physicians.17 Medical students also experience significant rates of depression and suicidality, with a recent meta–analysis reporting rates of depression of 33% in first year medical students.18 Yet evidence suggests that depression is undertreated in this population, perhaps due to concerns regarding a negative impact on the student's future career, poor insight, lack of time, or stigma.19 Greater knowledge of psychiatric disorders may contribute to reducing stigma, bringing down barriers to accessing health care, and improving mental wellness, not only for our patients, but also for ourselves.

References

12. UBC MD Undergraduate Curriculum Renewal [Internet]. Vancouver: UBC Faculty of Medicine; [cited 2016 May 31]. Available from: http://med.ubc.ca

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In this study, many sources of stress were identified, including ethical questions, trying to be certain of both prognosis and of the seriousness of the request for MAID, and lastly, feeling competent with the technical skills to carry out MAID. Being unprepared, both emotionally and clinically, for MAID can be a major source of stress. It is noteworthy that while physicians in this study found requests for MAID very challenging for many of the reasons described, none of those who assisted in a death regretted participating. Of special concern however, is that when faced with stress, none of the physicians sought support from colleagues or professional organizations, turning to spouses instead.

It is known that both dealing with death on a constant basis and dealing with very challenging deaths can have significant impact on clinicians. These impacts can include intense memories, self-doubt about competence and responsibility, and at times, a disconnection from patients. The direct effect of this may be burnout and depression. The indirect effect may be reduced compassion and communication with patients and families at times of great need.

From the perspective of pediatrics, my own specialty, the challenges raised by MAID will be significant. The key characteristic of pediatric practice is that the physician must engage with the parents and with the child in determining the course of treatment. While British Columbia has no medical age of consent, physicians are obligated to obtain at least a reasonable form of consent from children before starting treatment. It is not until adolescence, vaguely defined, that there is actual consideration of formal consent. Determining the best interests of a child, especially non-verbal, developmentally impaired children, is already a challenge. Adding MAID, which is effectively active euthanasia since children will not have the cognitive or physical competency to carry out an assisted suicide, will add to the complex challenges facing clinicians.

Care of children, especially in palliative/end-of-life situations, is highly contextual and socially linked. For example, withdrawal of ventilator support at end-of-life in neonatal intensive care units differs by location across three countries (The Netherlands, United States, and Canada). Differences include the use or non-use of neuromuscular blockade medications at the time of extubation. Therefore, decisions and approaches to MAID in pediatrics are unlikely to have consensus or consistency across centres, adding more uncertainty for clinicians.

How should physicians address the real possibility of stress related to MAID? One response is to increase knowledge about the practice of MAID—given that we now have Federal legislation, province-by-province guidelines are in place and the practice is already occurring. Physicians are already being informed about the guidelines and standards, the nature of requests, options for refusal, and lastly, the technical skills needed. This education, however necessary, will not be sufficient. Even with education, and even in jurisdictions where MAID has been well-established for over a decade, physicians continue to report significant personal stress.

Turning to one’s family members for support, while natural, is not sufficient. This approach assumes that a clinician has a partner to turn to or one who can be supportive. Physicians need to avail themselves of the many resources to support them in stressful situations. Each province has a physician support program. In British Columbia, the Physician Health Program of British Columbia operates a 24-hour support line and a website with resources: www.physicianhealth.com

As a general preventive measure, physicians should engage in the
types of wellness activities they routinely recommend to patients. The Ontario Medical Association has developed a number of resources through its Professionals Health Program, addressing physician wellness: http://php.oma.org/wellnessResourcesP.html

Whether we are ready or not, MAID will be here. We need to recognize the lessons from other countries that increased stress, and for some, increased self-knowledge and personal growth, will accompany this great change.

References
Models and mechanisms in neurodegeneration: Towards neuroprotective therapy in Huntington disease

Lynn A. Raymond, MD, PhD

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Neurological and psychiatric diseases are the leading cause of disability in Canada, and the prevalence of age-related neurodegenerative diseases is rapidly increasing with the aging population. Alzheimer disease (AD), Parkinson disease (PD), and Huntington disease (HD) share some common clinical and pathogenic features. All can impact cognition, movement, and mood at some stage of disease. Common mechanisms include insoluble protein deposits with impaired protein degradation, oxidative stress with mitochondrial dysfunction, and synaptic changes that occur before clinical manifestations. Although more rare than AD and PD, studying HD has advantages for leading the effort to develop neuroprotective therapies. Since HD is an inherited, monogenic disorder, the cohort of affected patients is well-defined. Predictive genetic testing identifies people destined to manifest HD, affording the possibility of intervention to delay disease onset and extend high-quality life. Additionally, genetically accurate mouse models of HD that exhibit phenotypes similar to human HD are invaluable for investigating pathogenic mechanisms.

Huntington disease

HD is inherited in an autosomal dominant fashion caused by expansion of a polymorphic CAG repeat in exon1 of the gene HTT, encoding the protein huntingtin with an expanded polyglutamine tract (mutant huntingtin; mHTT). Recent estimates of prevalence in populations of European descent have increased to 17.2 per 100,000, largely as a result of two factors—availability of the genetic test and increased life-span, however, certain populations in Asia and Africa have a much lower prevalence. Age of onset is inversely correlated with CAG repeat length. The disease manifests with a clinical triad of movement disorder, psychiatric disturbance, and cognitive decline, progressing to death 15-20 years following the motor diagnosis (for review, see 16). The movement disorder typically includes involuntary dance–like, or jerky, movement called chorea, deficits in voluntary motor coordination, and impairments of speech, swallowing, and balance. Depression and anxiety are the most common psychiatric manifestations and cognitive impairment involves frontal executive dysfunction, impaired recall, and deficits in learning. Currently, no disease–modifying agents are available and treatment is symptomatic. Striatal medium–sized spiny projection neurons, which receive glutamatergic afferents from the cortex and thalamus and project to other basal ganglia nuclei, are affected earliest and most severely by degeneration. As well, certain layers of cortex are also vulnerable. Recent reports using human autopsy brain tissue indicate that predominance of mood versus movement disorders correlate with more severe neuronal loss in striatal striosomes/anterior cingulate cortex versus primary motor cortex. Since predictive testing can identify healthy individuals carrying the mutation associated with HD, two world–wide observational studies have elucidated changes that occur prior to clinical diagnosis of HD. These include significant atrophy of the striatum—up to 40% loss at the time of diagnosis—as well as prominent loss of cortical white matter. Magnetic resonance spectroscopy (MRS) has shown chemical changes that distinguish controls from prodromal versus early stages of HD. Notably, advances in detection of femtomolar quantities of protein in cerebrospinal fluid (CSF) samples have revealed increasing levels of mHTT through the prodromal and early–to mid–stages of HD. Use of such biomarkers will enable interventional trials to delay onset of a clinical diagnosis.

Synaptic dysfunction: An early pathogenic feature of Huntington disease

Accumulating data implicate synaptic dysfunction as among the earliest changes in a variety of neurodegenerative disorders. Synaptic transmission changes occurring in the pre–manifest stages of several HD mouse models include: increased cortical excitability; altered balance of synaptic/extrasynaptic NMDA–glutamate receptor distribution on striatal spiny projection neurons, leading to downstream changes in survival/death pathways; altered plasticity at cortical–striatal synapses; and increased inhibitory synaptic activity. As the phenotype progresses, there is a profound loss of potassium conductances in astrocytes and striatal neurons, which increases neuronal excitability. Evidence suggests there are enhanced levels of dopamine in the early stages and reduced dopamine input in late stages of HD. These changes have been targeted by several drugs in recent clinical trials. Pridopidine, reportedly a “dopamine stabilizer” as a partial agonist at dopamine receptors, has completed two phase III studies with promising results in improving the movement disorder. Tetrabenazine, which inhibits vesicular dopamine transporter type 2 thereby depleting vesicular stores and reducing dopamine release, is highly effective in controlling chorea, but has significant side effects. Memantine, which selectively blocks extrasynaptic NMDA receptors while preserving activity of synaptic receptors, improves motor performance and skilled motor learning and protects against striatal degeneration in HD mice. Memantine has also been studied in a small phase II study of early HD with MRS/MRI and clinical endpoints (NCT01458170), but the results are not yet reported. Finally, deep brain stimulation of the globus pallidus, to re–balance opposing output pathways of the striatum, is in the early stages of investigation; a small number of patients found benefit on error/performance monitoring.

Mitochondrial dysfunction, altered calcium regulation, and metabolic changes in HD

Mitochondrial dysfunction, energy metabolism, oxidative stress, and calcium homeostasis have all been implicated in HD, as well as other neurodegenerative diseases. Huntington associates with mitochondria and mitochondrial respiration is impaired in cells expressing mHTT. Consistent with this, lower ratios of ATP to ADP have been identified...
in lymphoblasts from HD patients.\textsuperscript{36} Mutant HTT–induced reduction in PGC1-alpha, a master regulator of energy metabolism, has been implicated in mitochondrial dysfunction\textsuperscript{17} and drugs to counter this mechanism are under investigation in preclinical studies.\textsuperscript{36,39} Calcium–induced calcium release via IP3 receptors has been shown to be enhanced in HD mouse models,\textsuperscript{40} leading to depletion of endoplasmic reticulum calcium stores and a compensatory increase in calcium influx through plasma membrane store–operated channels, which may contribute to spine loss in striatal neurons.\textsuperscript{41} Three large clinical trials targeted some of these mechanisms. Creatine is thought to boost ATP levels, but a large phase III study, CREST-E, was recently halted for futility. Co-enzyme Q10, a component of complex 1 in mitochondria with anti–oxidant properties, showed promise in an initial study;\textsuperscript{42} however, a follow-up 5–year trial (2-CARE) was also halted for futility. Dimebon, which exerts neuroprotection, in part through a mitochondrial mechanism,\textsuperscript{43} showed no effect in a phase II study.\textsuperscript{44}

**Transcriptional dysregulation as a pathogenic mechanism in HD**

Transcriptional dysregulation is another central mechanism in HD pathogenesis. Huntingtonin has a role in shuttling between nucleus and cytoplasm and likely has important physiological roles in both compartments.\textsuperscript{45} However, with the CAG repeat expansion, mHTT has the capacity to interact with a variety of transcription factors in the nucleus and alter transcriptional regulation, which may be especially important at times of stress.\textsuperscript{46} Trafficking of mHTT can be modulated by post–translational modifications, including phosphorylation, sumoylation, and protease cleavage, which may play a major role in regulating its access to the nucleus.\textsuperscript{47} A downstream consequence of these changes is altered histone acetylation levels; histone deacetylase inhibitors have been tested in mouse models and a dose–finding study in humans.\textsuperscript{48} Further work is required in this area.

**Role of inflammation and altered protein homeostasis in HD pathogenesis**

Inflammation and clearance of misfolded proteins are also important areas of investigation in HD, as in other neurodegenerative disorders. Microglia (central nervous system) and macrophages (peripheral areas of investigation in HD, as in other neurodegenerative disorders. Inflammation and clearance of misfolded proteins are also important in HD pathogenesis.\textsuperscript{49} In humans.

**Conclusions**

In the early stages of disease, protecting synapses and re–balancing circuits, as well as mitigating the damaging effects of oxidative stress/ mitochondrial dysfunction, calcium dysregulation, and inflammation, provide promising avenues for further therapeutic development in a variety of neurodegenerative disorders. As well, enhanced clearance of misfolded proteins by using antibodies or upregulating endogenous cellular pathways (e.g. autophagy) represents a common target for AD, PD, and HD. With HD trials leading the way, therapies that use genetic tools to directly lower levels of damaged, misfolded proteins are becoming a real possibility and can be generalized to a number of heritable neurological disorders, including familial AD and PD.

**Acknowledgments**

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**Conflict of interest**

None to declare.

**References**


35. Milakovic T, Johnson GV. Mitochondrial respiration and ATP production are significantly impaired in striatal cells expressing mutant huntingtin. *J Biol Chem. 2005 Sep 2; 280(35):30773-82.


Mental illness and significant cognitive impairment among marginalized adults in Vancouver’s Downtown Eastside

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Around the world and close to home, health and wellness are experienced on a social gradient; consistently, those with lower socioeconomic position experience worse health.1 Mental illness and addictions are linked with social inequities, including poverty, stigma, and social exclusion. In Vancouver’s Downtown Eastside (DTES) neighbourhood, residents live in poverty and substandard housing, and many suffer from infectious diseases and substance use disorders.2 To address some of these health challenges, substantial health research has engaged the DTES community to reduce overdose deaths,3 transmission of HIV,4 and HIV–related mortality.5 Other efforts have examined harm reduction substitution therapies for substance dependence.6,8 The At Home/Chez Soi study demonstrated that providing subsidized housing and supports for homeless adults with mental illness improved housing stability9–11 and quality of life.9,12 However, this intervention had limited impact on daily substance use8,13 and mental health.8 The mental health needs of the community may be significant and under-supported.14 A Vancouver Police Department report highlighted that nearly half of calls to the police from the DTES were related to mental health.15 Police, rather than health care professionals, are often the first responders to mental health crises.15,16 Overall, the impact of mental illness in the community is largely unstudied and requires attention.

To address this gap, the Hotel Study was launched in 2008 to better characterize the health needs of individuals in the DTES who live in single room occupancy hotels, with a particular focus on mental health and cognitive function. This ongoing, naturalistic, longitudinal observational study follows over 400 adults living in marginalized housing monthly for ten years. The study comprehensively investigates mental, physical, and social health domains using objective and self–report standardized assessment tools. Participants are notified of clinically significant findings and connected with care. Here, we summarize findings from recent publications, addressing the consequences and risk factors for mental illness and areas for future investigation.

Severe consequences of mental illness

Mental illness is among the most common health challenges faced by the Hotel Study cohort. Vila–Rodriguez et al.17 examined viral exposure, substance dependence, neurological, and psychiatric illness, and found participants were living with a median of three co–morbid illnesses, including a particularly high burden of substance dependence (95%), hepatitis C infection (70%), psychosis (47%), and mood disorders (30%). Living with co–morbid conditions was associated with worse real–world functioning, including work productivity, independent living, and social relationships. Further, these potentially treatable illnesses might increase mortality risk. Participants (median age 44, 78% male) experienced a mortality rate over eight–times that of age– and sex–matched Canadians.18 Of the potentially treatable illnesses, psychosis or hepatitis C–associated liver dysfunction independently increased the risk of premature mortality among participants less than 55 years of age. For example, surviving to age 50 was more likely (94%) among those without psychosis, but less likely for those with psychosis (68%). Disturbingly, both psychosis and hepatitis C had extremely low treatment rates (32% and 0%, respectively).

Factors affecting mental health

Researchers and clinicians alike seek to better understand the intersecting biological, psychological, and social effects of factors affecting mental health. For example, substance use can have direct neurotoxic effects, impair decision–making, and lead to social isolation.9,20 Non–prescription drugs, such as methamphetamine, cocaine, and cannabis, can predispose and exacerbate mental illness. Methamphetamine and marijuana use may exacerbate the severity of positive symptoms, whereas opioid use may be associated with worse negative symptoms.21 Severe polysubstance use is also associated with worse physical, mental, and social health outcomes.22 Individuals frequently using substances associated with greater drug–related harms were more likely to experience persistent hepatitis C infection, substance–induced psychosis, and criminal activity. The examination of biological changes associated with substance use and mental illness by Willi et al.23 identified differences in brain structure associated with experiencing cocaine–induced psychosis compared to cocaine use without history of psychosis. Specifically, participants with psychosis had reduced structural integrity of white matter tracts within frontal and interhemispheric pathways (Figure 1). This aberrant myelination may result from abnormal neurodevelopment that increases vulnerability for psychosis, or may represent a greater sensitivity to the effects of chronic cocaine exposure.

The burden of exposure to biopsychosocial factors, such as social marginalization, viral infection, and substance use, may also impact the expression of psychosis, as well as cognitive processing. Giesbrecht et al.24 identified a unique psychosis symptom construct characterized by poor insight among Hotel Study participants that differed from previously examined populations with schizophrenia. Gicas et al.25 identified substantial cognitive impairment across the cohort, beyond what would be expected with aging. However, these deficits were not the same for everyone. Some participants demonstrated significant weakness in making decisions in the context of reward and punishment. This impairment may lead to impulsivity and engagement in behaviours that are immediately rewarding with less consideration for long–term consequences. These participants had high rates of heroin use and dependence, as well as a trend of greater injection drug use and HIV infection. These individuals may also have challenges with treatment adherence26 and may benefit from

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UBCMJ Volume 8 Issue 1 | September 2016 12
targeted psychoeducation for risk-taking behavior. Another group demonstrated global cognitive impairments, including verbal memory, attention, and mental flexibility, coupled with neurological signs that suggest overall poor brain integrity. This group had a widespread burden of factors, including viral infection, alcohol use, and psychotic symptoms. These individuals may benefit from highly structured care that assists with real-world tasks. Thus, understanding an individual’s relative strengths and weaknesses in cognitive processing may help to personalize and scale supports in care delivery.

Considerations for the future

Overall, the Hotel Study identified a high prevalence and significant impact of mental illness among marginalized housed adults in Vancouver’s DTES. Mental illness contributes to the compounding health challenges and premature mortality faced by these individuals, and is accompanied by impairment in brain structure and function. Illnesses, such as psychotic disorders, can be challenging to manage, especially for individuals restricted by access to care, stigma, and competing priorities when living in poverty with addictions. This research underscores the need to utilize innovative treatments and delivery methods to minimize barriers to quality care and prevent unnecessary death. For some individuals, depot antipsychotic medications can be effective in reducing dosing frequency and increasing contact with care providers, and have been shown to reduce relapse and hospitalization rates with similar mortality risk reduction as oral medications. Psychosocial interventions, such as cognitive therapy and assertive community treatment, may also improve the course of illness for individuals with severe mental health and addiction needs.

In the DTES, assertive community treatment program expansion is a priority for care delivery. In order to improve quality of life and wellness, our health and social service system must be prepared to address these complex needs and, as providers, we must advocate to redesign societal structures that hinder wellness and foster this social gradient of health inequity.

References

15. Wilson Burs F. Loss in recovery: How a lack of capacity in the mental health system is failing Vancouver’s mentally ill and draining police resources. Vancouver: Vancouver Police Department, 2008. 6 p.
The association between female–factor infertility and depression and anxiety

Nadine M. Rockwood, BSc(Hons)1; Amanda Pendergast, MD, CCFP, FCFP2

Citation: UBCMJ. 2016: 8.1 (14-16)

Abstract

Background Female–factor infertility is diagnosed when women of reproductive age are unable to conceive a pregnancy within 12 months of unprotected, frequent intercourse. Infertility affects between 11.5% and 15.7% of Canadian couples. The process of receiving a diagnosis and seeking treatment is often described as a devastating experience, which leads to psychological distress.

Objective A review of the literature was conducted to assess the association between an infertility diagnosis and the subsequent development of depression and anxiety symptoms among women.

Methods PubMed, PsycINFO, ClinicalKey, and Google Scholar databases were searched using the following MeSH terms and keywords: female–factor infertility, infertility, mental health, depression, and anxiety. Inclusion and exclusion criteria were established to identify pertinent articles for full-text review.

Results The majority of infertility research has been conducted in Europe and Asia using self-report questionnaires. The main finding from the research was that women experienced increased levels of infertility-related depression and anxiety, particularly with longer durations of infertility.

Conclusion Existing literature demonstrates an association between a diagnosis of female–factor infertility and the risk of development of depression and anxiety. Future research should focus on complementary qualitative research and quantitative research.

Introduction

Most women of reproductive age are able to conceive a pregnancy within 12 months of unprotected, frequent intercourse. However, for up to one in four women, conceiving and carrying a fetus is difficult and often unattainable, leading to an eventual diagnosis of infertility.1,2 Female–factor infertility, infertility specifically related to the female reproductive tract, has been identified worldwide.1,3 For example, 15.4% of Norwegian and 17.3% of Australian women experience infertility.4,5 Among Americans, prevalence rates are as high as 24.3% of nulliparous women.6 In Canada, infertility affects between 11.5% and 15.7% of couples, with an increased risk among women aged 35 to 44 years or who have given birth to less than two children.7 The inability for a woman to become pregnant or have a live birth is commonly described as a devastating experience, which leads to psychological distress.8,9 Therefore, the purpose of this literature review was to assess the relationship between female–factor infertility and mental health concerns. Specifically, the goal of this review was to examine the association between an infertility diagnosis and subsequent development of depression and anxiety symptoms among women.

Methods

The identification and review of articles that met inclusion criteria involved two phases. The initial search yielded 81 articles in PubMed, using the following medical subject heading (MeSH) terms: female infertility, psychology, depression, and anxiety. The search was limited to English language articles that included human subjects, adults between the ages of 19 and 44 years old, and female sex. The second review phase involved an expanded search of articles using PsycINFO, ClinicalKey, and Google Scholar. Keywords used in these searches included female–factor infertility, infertility, mental health, depression, and anxiety. Articles were selected based on inclusion and exclusion criteria. Articles were included in the review if they examined the effect of infertility on women's mental health and wellbeing. Articles were excluded if a mental illness diagnosis preceded an infertility diagnosis or was not directly related to infertility; if psychological factors were used as a predictor of treatment outcome; if modulating factors were assessed in relation to infertility and mental health; if only male infertility was assessed, and if only male responses to an infertility diagnosis were assessed. Additionally, articles were excluded if they were not original research that were peer-reviewed and published in research journals. Of a total of 92 articles, 12 studies met the established criteria and were selected for full-text review.

Results/Discussion

Study characteristics

Of the 12 articles reviewed, nine originated in Europe or Asia; the remainder were from Africa (n=2) or the United States (n=1) (Table 1). The majority of studies were published within the last seven years (n=8) and the remainder were published over ten years ago (n=4). The studies were predominantly cross-sectional with comparison groups (Table 1). Infertile patients were the focus participants in 11 of the 12 studies and were recruited from fertility treatment centres, hospitals, and physician clinics. Comparison groups were recruited from outpatient departments, physician clinics, or survey agencies and included healthy fertile women, pregnant women, or males within the same age ranges. The majority of studies assessed participants between 20 and 35 years of age. Participants were excluded if they had prior mental health concerns or remarkable past medical histories. Sample sizes ranged from 100 to 9200 participants, with the majority of studies assessing approximately 200 participants. All participants were assessed using self-reported questionnaires. Depression and anxiety were measured using various validated measurement tools (Table 1). Increased levels of infertility–related depression and anxiety were found in 11 out of 12 studies and 9 out of 12 studies, respectively (Table 2). Infertile women had clinically significant levels of depression and/or anxiety in over half of the studies (n=7; Table 2).

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**Depression**

Researchers suggest that women having difficulty conceiving are at a marked risk of developing depression after a diagnosis of infertility. The majority of patients (62%) attending fertility clinics had some form of depression, with 40% reaching mild levels and 22% reaching moderate levels of depression. In a similar demographic, only 10% of infertile women exhibited elevated depression scores; however, this was statistically greater than their male counterparts (1%). Compared to fertile participants, infertile patients were more likely to exhibit a greater number of depression symptoms and score significantly higher on depression scales. Researchers found that women with infertility exhibit a two-fold increase of depression scores compared to their fertile counterparts. Prevalence rates of severe depression following an infertility diagnosis are as high as 35.4%, compared to the prevalence of severe depression among fertile women within the same age group (19.4%). An additional study supports this finding, as more infertile patients (24.9%) demonstrated clinically significant depression symptoms than controls (6.8%). Conversely, Rostad and colleagues found no significant differences between the prevalence of depression among infertile women without a child (6.1%), infertile women with a child (6.5%), and fertile women (6.9%), in a similar European population. While depression did not appear to be a factor among the studied infertile Norwegian population, childless infertile women were significantly more likely to experience life dissatisfaction and poor health compared to their fertile counterparts. Therefore, the impact of infertility may manifest in forms similar to depression in this subset of infertile women. Limitations in the study may have led to the differences in the association of infertility and depression between articles. The study had a higher response rate from middle-aged women compared to younger women. Older women may have accepted their infertility diagnosis, whereas, younger women may have refused to participate due to the sensitive and emotional nature of the study. In addition to differing ages between participants, the data were antecedent. Therefore, confounding variables, time, and recall bias are of concern. Rostad and colleagues suggest that the impact of infertility may be stressor-specific, manifesting as a range of psychological symptoms, and recommend that stressor-specific measurements are employed when assessing infertile women.

**Anxiety**

Researchers suggest that infertile women are in jeopardy of developing anxiety. For example, anxiety cases were identified among 38% of infertile females awaiting assisted reproductive technology (ART), which was significantly greater than the 12% anxiety prevalence in the comparison group. In another study, a greater proportion of female infertile patients were diagnosed with moderate anxiety (15.5%) compared to fertile participants (7.9%). Only one study failed to find a significant difference between the prevalence of depression and anxiety in the treatment and control group; nevertheless, a trend toward increased anxiety was noted in women undergoing ART compared to age-matched, fertile women. This study also showed that childless infertile women were at a significant risk of suffering from phobic anxiety. These studies support the notion that infertile patients may experience increased anxiety compared to fertile women.

**Duration of infertility**

The duration of infertility may be an important risk factor for the development of depression and anxiety among women (Table 2). In

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**Table 2 | The number of reviewed studies with and without statistically significant findings as they relate to their categorized main results.**

<table>
<thead>
<tr>
<th>Results of Study</th>
<th># of studies reporting statistically significant findings</th>
<th># of studies reporting non-significant findings</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased depression scores among infertile patients</td>
<td>11</td>
<td>1*</td>
<td></td>
</tr>
<tr>
<td>Significantly high depression scores compared to comparison group</td>
<td>9</td>
<td>2*/2**</td>
<td>1</td>
</tr>
<tr>
<td>Increased anxiety scores among infertile patients</td>
<td>9</td>
<td>2***</td>
<td>1</td>
</tr>
<tr>
<td>Significantly high anxiety scores compared to comparison group</td>
<td>8</td>
<td>3*</td>
<td>1</td>
</tr>
<tr>
<td>Increased symptomology with duration of infertility diagnosis</td>
<td>6</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Clinically significant levels or diagnosis of depression/anxiety</td>
<td>7</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

*Comparison group was between infertile and non-infertile participants; however, further analysis compared infertile patients with and without children. 
**Comparison group was among cancer patients who had undergone fertility preservation.
***One study found a trend toward high anxiety scores. 
*8* Institute for Personality and Aptitude Testing; Zung Depression Scale /Zung Anxiety Scale, Profile Of Mood States, Women's Health Questionnaire, Center for Epidemiologic Studies Depression Scale.

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**Table 1 | Characteristics and overall profile of the 12 studies included in the literature review.**

<table>
<thead>
<tr>
<th>Overall Profile</th>
<th># of Reviewed Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Design</td>
<td></td>
</tr>
<tr>
<td>Cross sectional</td>
<td>8</td>
</tr>
<tr>
<td>Unidentified cross sectional</td>
<td>2</td>
</tr>
<tr>
<td>Longitudinal</td>
<td>2</td>
</tr>
<tr>
<td>Measurement tool used for assessing depression/anxiety</td>
<td></td>
</tr>
<tr>
<td>Beck Depression Inventory/Beck Anxiety Inventory</td>
<td>5</td>
</tr>
<tr>
<td>Hospital Anxiety and Depression Scale</td>
<td>3</td>
</tr>
<tr>
<td>State–Trait Anxiety Inventory</td>
<td>3</td>
</tr>
<tr>
<td>Symptom Checklist-90</td>
<td>2</td>
</tr>
<tr>
<td>Other *</td>
<td>5</td>
</tr>
<tr>
<td>Response rate reported</td>
<td>8</td>
</tr>
<tr>
<td>Control/comparison group</td>
<td></td>
</tr>
<tr>
<td>Fertile/non–fertile/pregnant females</td>
<td>7</td>
</tr>
<tr>
<td>Males</td>
<td>2</td>
</tr>
<tr>
<td>Other (unspecified, female fertility preservation patients)</td>
<td>3</td>
</tr>
<tr>
<td>Assisted reproductive technology treatment planned or pursued by patients</td>
<td>10</td>
</tr>
<tr>
<td>Location</td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td>6</td>
</tr>
<tr>
<td>Asia</td>
<td>3</td>
</tr>
<tr>
<td>Africa</td>
<td>2</td>
</tr>
<tr>
<td>America</td>
<td>1</td>
</tr>
</tbody>
</table>
one study, 43.4% of women experienced both depression and anxiety symptoms before beginning fertility treatment, with an additional 18.9% developing symptoms of depression and anxiety between the commencement and the conclusion of treatment. Moreover, the symptoms worsened over the duration of treatment. Droszdol and Skezypulec suggest that women struggling with infertility for three to six years were at a higher risk of developing mood and emotional disorders. Chiaffarino et al. demonstrated a positive association between a minimum four year diagnosis of infertility and depression or anxiety. Verhaak and colleagues found that infertile women experienced a significant increase in depression and anxiety between the first and second visits, with a significant increase in depression by the third visit. Conversely, Kee et al. found more severe depression symptoms at the first visit compared to subsequent visits. Further, some researchers have not found an association between infertility, depression, and anxiety at the five year mark. The inconsistencies between studies may be a function of culture or geography, as both articles with contradictory evidence showing decreased depression with longer periods of diagnosis assessed women from Asian populations. Infertility-associated depression and anxiety may be increased initially and taper with acceptance of the diagnosis or desensitization to the distress, allowing women to cope with prolonged emotional turmoil. It is conceivable that infertile women from Asian populations, who initially experience depression and anxiety with infertility, will experience resolution due to cultural influences and supports. Therefore, it is possible that women living outside Japan or Korea tend to experience a greater increase of depression and anxiety symptoms when nearing the end of infertility treatment/the longer they are infertile.

Limitations

A major limitation of the reviewed research articles is the self-report, survey study design. Infertility and mental health cannot be randomly assigned or investigated through quasi-experimental research; therefore, researchers ask participants to provide their subjective self-perceptions regarding their health and illness. Questionnaires are often designed with a few answer choices to each question; therefore, with limited options for answers, the data may be distorted and unrepresentative. Future research should include continuous scales, open-ended questions, and qualitative methods in adjunct to quantitative measurements.

The majority of articles reviewed were cross-sectional studies. This poses a limitation, as cause-and-effect inferences cannot be established. While researchers took precautions to exclude participants with a pre-existing history of mental illness, it is possible that the participants’ symptoms preceded their infertility diagnosis. Future research should implement a longitudinal design, with baseline depression and anxiety scores for comparisons. Moreover, numerous studies recruited participants from patient populations attending fertility treatment clinics and experienced low response rates. This may lead to a misrepresentation of the demographic and psychological wellbeing of infertile patients. Future research should aim to recruit patients from numerous different specialists and other resources within the population.

Additionally, there were limitations to the literature review. Survey tools to measure mental health and definitions of fertility differed across studies. Differences across studies complicate and impede comparisons of results across study samples. Moreover, recent research that met the inclusion and exclusion criteria was limited. Older articles may not be relevant to today’s population. Therefore, research on infertility is required globally, to address potential risk factors and associated psychological disorders among those who have difficulty conceiving.

Conclusion

The goal of the present literature review was to explore the relationship between female-factor infertility and depression and anxiety symptoms. The majority of the findings suggest that women may have an increased risk of developing depression and/or anxiety following a diagnosis of infertility. In particular, women who experienced a longer duration of infertility were more likely to experience greater levels of depression and anxiety. Duration of infertility, along with other potentially associated variables, should be considered when investigating in future research. As possible risk factors may confound infertility-related findings. The impact of infertility on women’s lives is profound, as it influences their overall wellbeing. Mental health and counseling services are important services to consider when assisting women with infertility.

References

The role of BDNF in Huntington Disease: A targeted analysis of 12 microarray studies

Ronald Xie¹; Sharon Yang²; Felix Ma³; Eric Y. Zhao, BSc²,³

Citation: UBCMJ. 2016: 8.1 (17-22)

Abstract

Objectives Huntington disease (HD) is a common hereditary neurodegenerative disorder. Pathogenesis is strongly associated with mutation of the protein huntingtin (HTT). Brain-derived neurotrophic factor (BDNF) is an essential growth factor in neurons and is downregulated in HD. This study focuses on the RE1-silencing transcription factor (REST)/BDNF pathway and provides statistical analysis on expression levels of many genes involved in this pathway in HD and normal subjects.

Methods Twelve recent microarray studies were systematically selected from the Gene Expression Omnibus (GEO). Over-representation analysis was performed on all assayed genes using the Database for Annotation, Visualization and Integrated Discovery (DAVID). Detailed analysis of genes involved in BDNF expression, delivery, and response was performed, and Fischer’s combined probability test was applied to combine findings across the 12 selected studies.

Results Our findings suggest downregulation of BDNF expression in HD-affected patients compared to controls. Analysis of the gene expressions of REST and AKT2 suggests that BDNF expression may be negatively correlated with REST expression and positively correlated with AKT2 expression.

Conclusions Our analysis demonstrates a systematic approach for the use of publicly available microarray data in the analysis of heritable diseases. Our findings suggest that changes in BDNF expression in HD may play a role in HD pathogenesis.

Introduction

Huntington disease (HD) is an autosomal dominant Mendelian disorder characterized by chorea, motor deficits, and cognitive changes. It results from CAG triplet repeat expansion in the huntingtin gene (HTT), with penetrance dependent on repeat number.¹ The age of onset varies greatly, but averages at roughly 40 years.⁴

Brain-derived neurotrophic factor (BDNF) is important in synaptic plasticity and neuronal survival in the striatum, a subcortical nucleus of the forebrain with an important role in HD. Downregulation of the gene BDNF has been implicated in HD pathogenesis,⁵ and BDNF-promoting therapies have been proposed for treatment of HD.⁶ This paper investigates the regulatory axis of BDNF expression and its downstream actions. As depicted in Figure 1, translation of mutant huntingtin protein (mHTT) from just one elongated HTT allele is sufficient to cause disruption of many key molecular pathways. One such pathway involves the RE1-silencing transcription factor (REST) which represses the expression of BDNF by binding to the neuron-restrictive silencer element (NRSE) on DNA.⁷ Normally, the HTT-bound product of REST fails to localize to the nucleus, thereby promoting expression of BDNF by disinhibition. In HD, the important interaction between mHTT and REST is lost, resulting in BDNF downregulation.

However, recent work has suggested that activation of Tropomysosin receptor kinase B (TrkB)-activated signalling cascades may be deficient in HD rather than BDNF delivery.⁸ TrkB is a BDNF-sensitive tyrosine kinase receptor encoded by the gene NTRK2 and has shown involvement in other neurodegenerative disorders such as Alzheimer’s Disease.⁹ It is an upstream activator of key pathways, including the Ras-Raf-Mek-Erk pathway and the PI3K-Akt pathway.¹⁰ Downregulation of TrkB may cause inactivation of downstream effectors despite sufficient expression, delivery and localization of BDNF. This raises the potential for a model of “BDNF insufficiency” due to TrkB dysregulation, rather than BDNF insufficiency alone. The Akt pathway, also known as the protein kinase B pathway, has been shown to regulate apoptosis, protein synthesis, and protein degradation. Activation of the Akt pathway has also been shown to be involved in HD¹¹ and has been linked to neuroprotective effects.¹² Therefore, it is important to distinguish between the causes of downregulation of Akt pathway in HD by examining the relative gene expression of BDNF, its receptor NTRK2, and that of other involved genes.

Leveraging publicly available data is an accessible and informative approach when exploring answers to well-defined biological questions. We propose a general approach for the use of publicly available microarray data and provide a proof of concept by applying it to the question surrounding the roles of BDNF and NTRK2 in HD. Microarray technology enables high-throughput quantification of gene expression at specific genomic loci. Publicly available microarray data, such as those found in the Gene Expression Omnibus (GEO), can be leveraged to rapidly test hypotheses. In this study, we aim to explore the gene expression underlying BDNF delivery and response systems in HD to determine whether they provide support for a model of BDNF insufficiency or BDNF insensitivity. We examined 11 genes relevant to BDNF delivery and response across 12 microarray studies, which were systematically selected from the Gene Expression Omnibus (GEO).¹³

The 11 genes of interest included genes encoding REST, proteins from the PI3K-Akt pathway, and receptors known to directly interact with BDNF, namely the Trk receptor family and the nerve growth factor receptor (NGFR). These genes were shortlisted based on local pathway analysis to provide preliminary evidence on the question of BDNF insufficiency vs insensitivity, while not diluting statistical power due to the relatively small number of available microarray studies. We analyzed their differential expression and employed multiple
Gene expression analysis

The expression of 11 genes involved in BDNF production, delivery, and response were extracted from data files for the selected HD and control groups of each study. For each study, a student’s t-test was performed to assess the statistical significance of the expression change between wild type and HD affected subjects. The p-values obtained from each study were then combined using the Fisher’s combined probability hypothesis testing to observe population level changes using data from the 12 shortlisted microarray studies. We also performed exploratory over-representation analysis of differentially expressed gene clusters. Our findings agree with previous work and raise questions for future study. As publically available high throughput data becomes more readily available, our approach may guide future studies investigating differential gene expression in HD.

Methods

Data usage and inclusion criteria

Data for this study were taken exclusively from publicly available data repositories. This study therefore did not require ethics approval. Data were downloaded from GEO via their online interface at http://www.ncbi.nlm.nih.gov/geo/. Raw microarray values were parsed and processed using a custom script (parsegeo.py, see supplemental data). Processed data and all subsequent statistical analyses can also be downloaded in the supplemental data for this paper.

GEO studies were shortlisted by searching for the term “Huntington Disease” and including all studies on Homo sapiens and Mus musculus species. Microarray data and sample preparation methodologies from the resulting 17 studies were carefully reviewed for inclusion in our analysis. Of the 17 studies, a total of five were excluded. One human study (GDS4541) was excluded as the tissue studied was whole blood rather than brain. Four mouse studies (GDS2391, GDS4542, GDS4533, and GDS3178) did not have study groups sufficiently relevant to HD. Of the remaining twelve studies, nine were collected from M. musculus and 3 from H. sapiens. Due to the small number of human studies, only M. musculus studies were used for statistical analyses, whereas H. sapiens studies were referenced afterwards to check for concordance of results with findings from the M. musculus studies. In each study, the untreated control group was compared with the HD model group. In studies containing more than one classification of HD, the model producing the most severe phenotype was chosen. Table 1 reports the study IDs and group names for the selected HD and control cohorts, which can be used to replicate this study using data available publicly at http://www.ncbi.nlm.nih.gov/geo/. After these exclusions, a total of 108 HD affected subjects and 118 normal controls across the 12 studies remained.

Table 1 | Selected studies and the names of study groups utilized in this meta-analysis. All data are publicly available via the Gene Expression Omnibus at http://www.ncbi.nlm.nih.gov/geo/, and can be identified using their GEO Study Accessions and available metadata.

<table>
<thead>
<tr>
<th>GEO Study Accession ID</th>
<th>Organism</th>
<th>HD Group Name</th>
<th>Control Group Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>GDS2169</td>
<td>M. musculus</td>
<td>Nuclear polyQ (n = 11)</td>
<td>Control (n = 24)</td>
</tr>
<tr>
<td>GDS2464</td>
<td>M. musculus</td>
<td>Mutant huntingtin transgene (n = 4)</td>
<td>Wild type (n = 4)</td>
</tr>
<tr>
<td>GDS2911</td>
<td>M. musculus</td>
<td>Untreated (n = 3)</td>
<td>Wild type (n = 6)</td>
</tr>
<tr>
<td>GDS2912</td>
<td>M. musculus</td>
<td>R6/1 transgenic (n = 9)</td>
<td>Wild type (n = 9)</td>
</tr>
<tr>
<td>GDS3620</td>
<td>M. musculus</td>
<td>YAC128 (n = 10)</td>
<td>Wild type (n = 8)</td>
</tr>
<tr>
<td>GDS3621</td>
<td>M. musculus</td>
<td>YAC128 (n = 10)</td>
<td>Wild type (n = 8)</td>
</tr>
<tr>
<td>GDS3935</td>
<td>M. musculus</td>
<td>Hdh GAC knock-in Q111/Q111 (n = 12)</td>
<td>Wild type (n = 12)</td>
</tr>
<tr>
<td>GDS4534</td>
<td>M. musculus</td>
<td>Hdh Q111/111 (n = 6)</td>
<td>Hdh+/+ (n = 6)</td>
</tr>
<tr>
<td>GDS717</td>
<td>M. musculus</td>
<td>R6/2 (n = 7)</td>
<td>Wild type (n = 6)</td>
</tr>
<tr>
<td>GDS1331</td>
<td>H. sapiens</td>
<td>Symptomatic HD (n = 12)</td>
<td>Healthy Control (n = 14)</td>
</tr>
<tr>
<td>GDS1332</td>
<td>H. sapiens</td>
<td>Symptomatic HD (n = 12)</td>
<td>Healthy Control (n = 14)</td>
</tr>
<tr>
<td>GDS2887</td>
<td>H. sapiens</td>
<td>Moderate HD (n = 12)</td>
<td>Healthy Control (n = 10)</td>
</tr>
</tbody>
</table>
Figure 2 | Dot plots of differential expressions of the 6 most notable genes across 12 studies of Huntington disease (HD). Studies were systematically selected from the Gene Expression Omnibus. Microarray data from the 12 selected studies was used to quantify differential expression. Error bars were calculated via error propagation and reflect 95% confidence intervals. When considered independently, any interval not containing 0 implies a statistically significant difference between HD and control groups within the given study. Fisher's combined probability test was used to combine the p-values of individual studies and calculate an aggregate chi squared and p-value for the differential expressions of each gene. Human studies are shown in yellow, and mouse studies in black. Human studies were not used in statistical analysis.
test to obtain one p-value for each gene.\textsuperscript{20,21} The Fisher’s combined probability test is an omnibus test that can be suitably applied in meta-analyses to determine whether a global null hypothesis can be rejected given the results from multiple independent studies. This test differs from other common multiple hypothesis testing methods, such as the ANOVA f-test, due to its robustness against systematic differences across studies arising from usage of different materials, protocols, and microarray sensitivities, and other factors, as long as the tested global hypothesis can be applied to the datasets of each individual study in the same way. Consequently, even if an included study is addressing another hypothesis altogether, as long as the tested global hypothesis can be applied, data from the experiment can be leveraged for meta-analysis. Furthermore, it is not necessary to assume homogeneity of variance across the tested null hypotheses as in the ANOVA f-test. This especially applies to instances where sample sizes differ substantially (often the case for publically available microarray data), where the homogeneity of variance assumption falls apart for ANOVA f-test. Taken together, using the Fisher’s combined probability test allows the inclusion more publically available datasets and provides a meaningful way to evaluate a global null hypothesis from datasets produced by independent individual studies.

As the Fisher’s combined probability test does not account for the directionality of findings, the p-values of the studies showing change opposite to the hypothesized direction were assumed to be 1.0 (the maximum possible p-value). This allows for simplification of the calculation without relaxing the conditions for significance, yielding a conservative estimate of the final product. The percentage change in the expression level of each gene for each study was calculated and plotted to further visualize the result of the Fisher’s combined probability tests. Error bars for percent changes in expression were determined by error propagation calculation and represent 95% t-distribution confidence intervals.

Whereas expression changes for individual samples is commonly reported as fold changes, the mean expression changes reported here are reported as percentage changes. This is because our reported expression values arise from mean values of studies containing three to twelve HD samples and four to twenty four controls each. By the central limit theorem, the standard error of the mean is substantially less variable than the standard deviation of a single subject. This study aims to identify population level trends in HD, which are much smaller in magnitude than drivers of individual disease cases.

Over-representation analysis of gene expression change
For every gene assayed in the included microarray experiments, the natural logarithm of the fold change in gene expression was calculated and averaged across studies. Any gene with a fold change of greater than two-times was included. Over-representation analysis was performed using the Functional Annotation Clustering tool in DAVID with the inclusive set of all genes assayed by the microarrays as the background. Upregulated and downregulated genes were analyzed as two separate sets.

Results
Differential expression was observed in BDNF, AKT2, and NGFR, however only BDNF displayed concordance in the direction of change between studies. NTRK3 also displayed a concordant trend toward upregulation, but without statistical significance (p = 0.062). Figure 2 shows the 95% confidence interval of percentage change for each gene in each study.

Figure 3 | Scatter plots of mean percent change in expression in HD in nine mouse studies reveal a positive trend between BDNF and AKT2 (r = 0.58, p = 0.11) and a significant negative correlation between BDNF and REST (r = -0.63, p = 0.029).

Differential expression of BDNF
The nine murine studies examined displayed decreased mean BDNF expression in HD when compared with normal controls. Downregulation was concordant in seven of the nine studies. When observed individually, decreased BDNF expression in one study (GDS2912) was statistically significant (p = 0.001), and two other studies (GDS2169 and GDS3620) were nearly significant (p = 0.076 and p = 0.075 respectively). The studies showed a range from 2% to 42% decrease in BDNF expression with a median decrease of 9.9%. Two studies displayed increased BDNF expression of 5-6%. Fisher’s combined test suggests BDNF downregulation when combining our nine murine studies (p = 0.022). Although changes in REST expression were not statistically significant, the change in mean BDNF expression displayed a significant negative correlation (p = 0.029, r = -0.66) with REST expression change (Figure 3).

Expression changes in NTRK3, PTEN and the AKT pathway
NTRK3 expression displayed a near-significant upregulated trend (p = 0.062) with concordance in six out of nine murine studies, with a range of 2.5% to 16.5% increased expression and a median increase of 5.5%.

PTEN expression showed upregulation in six out of nine studies ranging from 2.5% to 15.4%, with a median increase of 5.6%. Fisher’s combined probability test returned a p value of 0.114. The low chi-
squared value is mostly driven by the high variability of three studies (GDS2464, GDS2912, GDS3620, see supplemental data for a graph of PTE:N expression).

Of the three AKT family genes profiled, AKT2 was the only one which displayed statistically significant differential expression in HD (p = 0.016). Expression was decreased in five out of nine murine studies, ranging from 4% to 35% (median 8%) downregulation. The other four studies showed small increases in expression in HD ranging from 0.17% to 1.3%. NGFR, a negative regulator of the Akt pathway, displayed decreased expression in HD (p = 0.015). However, the results were discordant and appear to be driven by one study (GDS2464).

Results of over-representation analysis of differentially expressed genes

Functional clusters of upregulated and downregulated genes suggest changes in a variety of functions in HD-affected cells (Table 2). Key upregulated processes of interest include metal binding and carbohydrate metabolism. Downregulated processes include immunospecific binding and secretory granule formation among others.

Discussion

Cross-study analysis of the expression in the BDNF and Akt signalling cascades has yielded findings informative of the role of these key pathways in the pathogenesis of HD. Downregulation of BDNF and a negative trend between BDNF and REST expression changes were observed, which agrees with the canonical model of decreased BDNF production in HD. A nearly significant trend was observed in NTRK3, but with small effect size. TrkC, the protein encoded by NTRK3, is not thought to interact directly with BDNF, but does bind to neurotrophic ligands and act on the Akt pathway.

Despite extensive research surrounding the canonical model of BDNF downregulation in HD, recent published work by Plotkin et al. suggests that its delivery to the neurons of the striatum and activation of receptors are normal. Our results did not show any significant changes in expression for NTRK2. Furthermore, PTE:N, an inhibitor of the PI3K-Akt pathway downstream of TrkB, was found to be upregulated with near statistical significance, both of which are concordant with the findings of Plotkin’s study and alludes to the proposed hypothesis that BDNF-related signal transduction may be impaired in HD. However, our findings suggest that the possibility of decreased BDNF expression is not to be discounted. Either hypothesis is supported by evidence that the Akt cascade may be downregulated in HD, and further study is warranted to describe how Akt activation varies with BDNF expression. However, it is worth noting that expression of FASL, a pro-apoptotic factor whose transcription is inhibited by the Akt pathway, was not found to be induced in HD. The genes AKT1 and AKT3 also showed no significant downregulation. These results may potentially weaken our findings relating to the downregulation of Akt2. They may be caused by lower than optimal sample size or more interestingly, may imply another layer of complexity in the interplay between BDNF, Akt and downstream effectors. Ultimately, our most striking finding is the downregulation of BDNF. Even though only three out of the nine studies individually possess confidence intervals not crossing 0, as a whole data combined across the multiple studies revealed an overall statistically significant difference, with strong concordance between studies. This was observed with high effect size and correlation with REST expression. Not only is BDNF downregulation observed in seven of nine murine studies, it is also observed in all three human studies examined (GDS1331, GDS1332, and GDS2887), which hints at a possible common mechanism in human disease.

As nuclear levels of REST are regulated post-translationally via binding to HTT, it is unclear why REST expression would be increased. This study uncovers preliminary evidence of REST overexpression in HD as a potential contributing mechanism of BDNF downregulation which should be replicated and further investigated. Our findings in NGFR, AKT2, and NTRK3 are suggestive of changes in HD, but fail to conclusively demonstrate that transcription-level changes in these genes play active roles in pathogenesis. Further investigation is necessary with greater sample size in order to uncover potential effects.

ORA suggested many affected functions in HD. The upregulation of metal binding proteins points to potential toxicity arising from the binding of metals in neuronal cells. The downregulation of immune targeting processes is in line with the role of mHTT in impairing immune cell migration. Of particular note to this study, the downregulation of genes involved in secretory granule formation may suggest a role of decreased delivery of BDNF among other cell products to their targets.

This paper lays out an approach for the systematic cross-study analysis of a selected set of genes. A limitation of this analysis is its focus on mouse models, which may not demonstrate direct transferability to human disease. Therefore, these results warrant further study in the setting of human HD. Furthermore, the nine mouse studies included utilize different mouse models to represent diseased states, and so may vary significantly in their gene expression profiles. For example, R6/1 and R6/2 mice (used in studies GDS2912 and GDS717) employ truncated mHTT N-terminal fragments with 116 and 144 CAG repeats, respectively (although R6/2 mice can develop up to 250 CAG repeats over time). On the other hand, Hdq111 mice (used in GDS4534 and GDS3935) employ a full-length HTT knock-in with 111 CAG repeats.

Table 2 | Upregulated and downregulated functional gene clusters based on over-representation analysis using DAVID. A set of significantly upregulated and downregulated genes were used as input for functional classification, and the most significant five upregulated and downregulated clusters are shown.

<table>
<thead>
<tr>
<th>Downregulated Clusters</th>
<th>Enrichment Score</th>
<th>Benjamini P-value Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regulation of cell growth, size, transcription, and metabolism</td>
<td>4.175</td>
<td>7.9 x 10^{-5} – 0.079</td>
</tr>
<tr>
<td>Immunospecific binding and plasma membrane proteins</td>
<td>3.704</td>
<td>2.3 x 10^{-4} – 0.57</td>
</tr>
<tr>
<td>Histone proteins, nucleosome organization, and DNA packing</td>
<td>2.248</td>
<td>7.9 x 10^{-5} – 0.97</td>
</tr>
<tr>
<td>Signal transduction: Rhodopsin like G-protein coupled receptors</td>
<td>4.132</td>
<td>7.9 x 10^{-4} – 1.0</td>
</tr>
<tr>
<td>Secretory granules and vesicle formation</td>
<td>1.432</td>
<td>7.9 x 10^{-4} – 1.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Upregulated Clusters</th>
<th>Enrichment Score</th>
<th>Benjamini P-value Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Innate immune antimicrobial defense: lysozyme, hydrolase etc.</td>
<td>3.197</td>
<td>1.48 x 10^{-3} – 0.97</td>
</tr>
<tr>
<td>Cation/transition metal binding: Binding of zinc ions in particular.</td>
<td>3.074</td>
<td>1.0 x 10^{-4} – 0.089</td>
</tr>
<tr>
<td>Carbohydrate metabolism: Glycoside hydrolase family.</td>
<td>4.175</td>
<td>7.83 x 10^{-7} – 0.089</td>
</tr>
<tr>
<td>Sterile alpha motif.</td>
<td>3.504</td>
<td>5.00 x 10^{-4} – 0.089</td>
</tr>
<tr>
<td>Ribosomal protein subunit.</td>
<td>1.945</td>
<td>6.02 x 10^{-5} – 0.96</td>
</tr>
</tbody>
</table>

This study uncovers preliminary evidence of a possible common mechanism in human disease.
YAC128 mice (used in GDS3620 and GDS3621) fall into a third class, possessing full-length human HTT with 128 repeats but in a transgenic rather than endogenous model. Different modeled disease stages and CAG repeat lengths may account for some variability in the effect sizes of the included studies. Mouse strains also possess different genetic backgrounds and may express different disease phenotypes from similar genetic alterations. Standardization is often a challenge, given the phenotypic variability that exists even within a single strain, such as in R6/2 mice.26

However, a potential strength of our methodology is in the synthesis of findings from different models irrespective of disease stage. This strength will be increasingly pronounced with larger numbers of available studies. Due to small sample sizes, we intend for this study to serve primarily as a proof of concept for our methodological approach. In order to allow for interpretation of findings, p-values were not adjusted for multiple hypothesis testing. When a Benjamini-Hochberg adjustment is performed, the findings derived from Fisher's combined probability test are not statistically significant at the 95% confidence level. Since the Benjamini-Hochberg adjustment is often necessary to reduce the probability of false positive findings, we approached interpretation of these results with caution and considered multiple sources of evidence including statistical analysis, concordance between studies, and correlation data when drawing conclusions. More importantly, this paper highlights a generalizable methodological approach which may be applied to larger study sets with success as a convenient screen for early hypothesis generation and testing.

HD remains an incurable disease with a heavy associated social burden, affecting 5 to 10 per 100 000 people worldwide.27 In this study, we investigated the expression of many key genes implicated in the pathogenesis of HD. Changes in expressions of these genes may elucidate possible explanations for the loss of BDNF-dependent post-synaptic plasticity. Our findings provide evidence for the role of impaired BDNF expression, delivery, and response in HD pathogenesis, in coordination with the REST-BDNF system. They also hint at concomitant downregulation of AKT2, and thereby possible involvement of the Akt pathway, which has known roles in HD. These findings support the canonical model of BDNF downregulation and insufficiency. The use of gene expression analysis across studies remains a powerful method for investigating the molecular biology of well-characterized diseases. We have utilized these methods to shed light on processes in HD which inform on cell function, disease formation, and pathology.

Supplementary files are available online at ubcmj.com

References
Temporal changes in age at onset of multiple sclerosis: Importance of controlling for equal observation time

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Abstract
Background Previous studies examining whether changes in the age of multiple sclerosis (MS) onset have occurred over time have yielded inconsistent findings.

Objectives We investigated temporal trends in MS age at onset in three Canadian provinces and assessed the effect of controlling for equal observation time between birth year groups.

Methods We included 9459 MS patients from MS clinic databases in British Columbia (BC, n=5423), Manitoba (MB, n=1419), and Nova Scotia (NS, n=2617). Birth years were grouped into five-year blocks and analysed via ANOVA and linear regression to assess temporal trends in age at onset. The complete cohort included all MS patients. The restricted cohort allowed comparable observation times for each birth year group and included patients who had reached age 40 and who had MS onset at age 40 or younger.

Results The complete cohort showed a steep decline in age at onset (averaging 2.0 years between birth year groups), from 37.0±10.8 years (1941-1945 births) to 28.0±6.4 years (1966-1970 births), p<0.001. In the restricted cohort (n=6003), only BC patients showed a significant decrease in the mean age at onset (averaging 0.3 years between birth year groups): 29.6±6.5 years (1941-1945 births) and 27.4±5.8 years (1966-1970 births), p<0.001. No significant decrease in age at onset was evident in the NS or MB restricted cohorts.

Conclusions If the age at MS symptom onset has changed in the last four decades, shifts have been small. Temporal changes in age at MS onset between birth cohorts can be inflated without due consideration to comparable observation time.

Introduction
Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system that affects over 2.5 million people worldwide. The underlying etiology is not well understood, although it is likely a combination of environmental and genetic factors.1,4 It can be speculated that if any of the environmental factors were to change, an impact on the age at onset (i.e. age at first symptoms) might be seen. Several studies have reported temporal changes in the demographic characteristics of MS, including a decreasing average age at onset.5,6 This has prompted investigations into the observed changes in MS age of onset, the timescale of which might suggest a shift in etiologically relevant environmental factors.2 The age at which MS symptoms first begin ranges from early childhood to late adulthood. However, the average age at MS onset is widely quoted as being around 30 years of age, with most presenting with MS between the ages of 20-40 years.5,6

Previous studies that have investigated differences in the age at MS disease symptom onset between different birth year groups have reported that the average age at onset decreased over time.5,6 However, a follow-up study by one of these groups demonstrated that analyses without equal observation time could lead to spurious findings suggesting changes over time, or differences between generations in age at disease onset;7,8 these differences disappeared once the adjustment for equal observation time was applied.10 Without adjustment for unequal follow-up time, younger (more recent) birth cohorts would appear to have a younger average age at onset because they had not had the opportunity to reach an older age by the end of follow-up. We aimed to assess the potential effects of restricting the cohort with equal observation times and to determine whether changes in age at onset were evident between birth cohorts.

Materials and methods
Data Sources
This study utilized data collected from three cohorts of MS patients from three different provinces in Canada: British Columbia (BC), Manitoba (MB), and Nova Scotia (NS). Data were collected prospectively in BC and NS, while in MB, data were collected through a combination of chart reviews and prospective data collection. Each database contained information on all MS patients attending the MS clinics within the respective province. These databases have been used extensively for research purposes to address questions on MS.5,6,11-15 Briefly, the British Columbia Multiple Sclerosis (BCMS) database contains details on patients visiting one of four MS clinics in BC since the opening of the first clinic in 1980. These four clinics are based in Vancouver, Victoria, Kelowna, and Prince George, and were the only MS specialty clinics in the province until the end of 2004. A fifth clinic, which opened in 2005, is not linked to the BCMS database. The MB MS database has collected information on patients attending the University of Manitoba’s MS clinic (the only MS clinic in the province) since 1998. The Dalhousie MS Research Unit (DMSRU) database in NS collates information on individuals attending the sole outpatient clinic in NS that specializes in MS care since 1980. For the purposes of this study, each site provided demographic and clinical data (year of birth, age at MS onset, and sex) to the end of 2008 (the predetermined study endpoint).

Selection of study cohorts
All patients with a diagnosis of definite MS by Poser or McDonald criteria2,5,16 a recorded MS symptom onset date, and year of birth between 1941 and 1980 were selected from each province’s database.
All individuals fulfilling these criteria were included in the ‘complete cohort’; patients were excluded if they were born before 1941 or after 1980, and if they were missing the MS symptom date of onset. From this complete cohort, a restricted cohort was selected to ensure equal observation time; cases were restricted to those with a birth year between 1941 and 1967 (i.e. those who were at least 40 years old by the study end) with an MS age at onset <40 years. Birth years were categorized into 5–year intervals where possible, from 1941-1945 to 1976-1980 for the complete cohort, and from 1941-1945 to 1966-1967 for the restricted cohort. The last category for the restricted cohort included only those born in 1966 and 1967 as per the time restriction.

This study was approved by the University of British Columbia’s Clinical Research Ethics Board (approval # H11-00386).

Statistical analyses
Analyses were performed on the complete and restricted cohorts in the combined dataset and stratified by individual province. The demographics (sex and birth year) and clinical characteristics (age at symptom onset) of all patients from each of the provinces were reported descriptively.

To explore whether there were observable trends in MS age at onset over time, the mean age at onset was compared between the birth year groups using Analysis of Variance (ANOVA). The association between birth year and the age at MS onset was also examined by linear regression analysis with birth year treated as a continuous variable. Alpha (α) was set at 0.05. All analyses were performed using IBM SPSS Statistics 22 (IBM Corporation 1994, 2015).

Results
In total, 9459 individuals met the inclusion criteria; 5423 from BC, 1419 from MB, and 2617 from NS. The demographic and clinical characteristics of participants are shown in Table 1. The proportion of women was comparable between the sites and between the complete (74.3% female) and restricted (74.7% female) cohorts. The mean age at onset was also similar across provinces; the average MS age at onset was 31.8 years in the combined complete cohort and 28.9 years in the restricted cohort (Table 1).

Figure 1 | Graphs of the combined data and each of the three provinces separately showing the mean age at onset (with 95% confidence intervals) by birth year group for the broad cohort and for the restricted cohort. The lines represent the results of regression of age at onset on birth year (as a continuous variable).
The results from the linear regression analyses of the complete cohorts indicated that the mean age at onset decreased as the birth year increased. This was consistent for the combined cohort and each of the individual provincial cohorts. However, when the analyses were repeated with the restricted cohorts, the difference in age at onset decreased considerably for both the combined cohort (1.4–year age difference between the earliest and latest birth year groups) and BC cohort (2.2–year age difference between the earliest and latest birth year groups) (see Table 2 and Table 3). There was no statistically significant association between birth year and age at onset for the NS or MB restricted cohorts (Table 3).

**Discussion**

Using equal observation times, we found no evidence of a change in the MS age at onset over a 27–year period (birth cohort) in two Canadian provinces (Manitoba and Nova Scotia). While the MS age at onset might have decreased somewhat with time in BC, this decrease was not comparable to the magnitude of change in age at onset reported by others. An overall small decrease was seen in the combined cohort, which is presumed to be driven by the larger BC cohort. These findings are in contrast to other studies that have not all allowed for equal observation time, including a Sardinian cohort study that reported large differences between the mean age at MS onset (41 years in the most remote decade of birth and 22 years in the most recent decade of birth), and a Spanish cohort study that found a median MS age at onset of 30 years in the most remote birth decade and 22 years in the most recent birth decade.

Reasons for the small decrease in MS age at onset observed in BC are unknown. However, possible reasons might include the changing ethnicity of the BC population over recent years and the greater ethnic diversity of BC compared to MB and NS, as well as an increased awareness of MS symptoms. Although the underlying etiology of MS is not well understood, it is believed to involve a complex interaction of genetic and environmental factors. The environmental factors that have been implicated include sunlight exposure, Vitamin D, timing of infection with Epstein Barr Virus, and smoking exposure to any or all of these factors is likely to have changed over recent decades, but the role that such changes play in shortening the time between birth and onset of MS would be speculative.

It is important to assess changes in age at onset appropriately because a trend toward decreasing age at onset would point to potential changes in environmental factors that influence the onset of MS clinical symptoms. A true reduction in the age at onset would also affect estimates of incidence and prevalence and changes in these measures over time. Furthermore, study findings that suggest that an increasing ratio of remitting-relapsing MS (RRMS) to primary progressive MS (PPMS) over time might be based on spurious results if insufficient follow–up time was allowed for people to develop PPMS, since individuals with PPMS typically have a later disease onset.

We were fortunate to have access to three large Canadian cohorts of MS patients with a heterogeneous population, which lent added power to our study. This allowed us to create a large combined dataset that included MS patients from three provinces in Eastern, Central, and Western Canada. The cohorts were followed for up to 28 years of ascertainment and 4 decades of birth years. This allowed for the identification of potential heterogeneity between geographic regions and populations of Canada while the follow–up period allowed for the assessment of trends over a significant period of time.

While the three databases captured most MS patients, a limitation of this study is that they did not capture the whole MS population in their respective provinces. Although it is not possible to determine the exact coverage, previous studies have estimated that the BCMS database captures approximately 60-80% of MS patients in BC and the NS database captures between 67-83% of MS patients in NS. The proportion of cases captured in MB is expected to be comparable to NS and BC. It is possible that age at onset trends are different among patients that did not attend these clinics, although the impact of unequal observation times is expected to be the same. For future birth cohort studies, the inclusion of more recent generations and more data from other provinces (if available) would be optimal.

The databases in BC and NS were populated prospectively, while in MB, data were collected through a combination of chart reviews and prospective data collection. Clinical information in the MB charts

### Table 1 | Characteristics of the MS cohort from British Columbia, Manitoba and Nova Scotia

<table>
<thead>
<tr>
<th>Birth year:</th>
<th>British Columbia</th>
<th>Manitoba</th>
<th>Nova Scotia</th>
<th>All Provinces</th>
</tr>
</thead>
<tbody>
<tr>
<td>1941-1945</td>
<td>651 (73.7)</td>
<td>400 (73.8)</td>
<td>78 (73.6)</td>
<td>37 (73.4)</td>
</tr>
<tr>
<td>1946-1950</td>
<td>933 (75.7)</td>
<td>168 (71.8)</td>
<td>91 (71.8)</td>
<td>365 (72.3)</td>
</tr>
<tr>
<td>1951-1955</td>
<td>1056 (77.3)</td>
<td>232 (75.8)</td>
<td>148 (75.8)</td>
<td>434 (75.8)</td>
</tr>
<tr>
<td>1956-1960</td>
<td>969 (79.4)</td>
<td>258 (75.8)</td>
<td>176 (75.8)</td>
<td>472 (75.8)</td>
</tr>
<tr>
<td>1961-1965</td>
<td>759 (72.6)</td>
<td>237 (75.8)</td>
<td>204 (75.8)</td>
<td>450 (75.8)</td>
</tr>
<tr>
<td>1966-1970</td>
<td>547 (75.0)</td>
<td>193 (75.0)</td>
<td>72 (75.0)</td>
<td>319 (75.0)</td>
</tr>
<tr>
<td>1971-1975</td>
<td>343 (N/A)</td>
<td>140 (N/A)</td>
<td>72 (N/A)</td>
<td>185 (N/A)</td>
</tr>
<tr>
<td>1976-1980</td>
<td>165 (N/A)</td>
<td>113 (N/A)</td>
<td>162 (N/A)</td>
<td>440 (N/A)</td>
</tr>
</tbody>
</table>

*Sex: female, n (%)| 3995 (73.7) | 2616 (73.8) | 1055 (74.4) | 558 (76.6) |
| Birth year: | 29.3 (6.76) | 258 (6.76)  | 969 (6.76)  | 32.4 (6.76) |

*Age at onset: Mean (SD)*

| 31.4 (8.98) | 28.8 (6.46) | 32.2 (9.72) | 29.3 (6.76) |

*Data only available between 1966-69 for the restricted cohort*
was collected at each clinic visit by the MS specialist neurologist (i.e. by a comparable method to the data collection methods in BC and NS). Therefore, we do not expect that differences in data collection methods influenced our findings and conclusions.

Due to the inevitable delay between MS symptom onset and the date of diagnosis, the onset date of MS symptoms is typically collected retrospectively by patient recall. The accuracy of this recall might be influenced by many factors, including the delay to medical recognition or diagnosis, and symptom severity at onset. This might also lead to apparent changes in age at onset over time.

We used a smaller birth year interval for the most recent (1966-1967) birth group in the restricted cohort analyses rather than the five-year interval used for the other groups. However, the 1966-1967 birth cohort still included 439 subjects, a number that was comparable to that in the 1941-1945 restricted cohort (557 subjects). Both of these smaller birth cohorts included sufficient patients, allowing adequate power to address the objectives of this study.

By using three MS cohorts from three different Canadian provinces, we have demonstrated how estimates of change in the age at MS symptom onset between birth year groups over time can be significantly inflated when observation time differed, or was not controlled for, between birth cohorts. Moreover, attempts to address this question with birth cohorts of varying observation time can introduce bias. It is therefore important to ensure comparable observation times and equal opportunity to develop symptoms when assessing trends in the clinical characteristics of MS.

References
Credible, centralized, safe, and stigma–free: What youth with bipolar disorder want when seeking health information online

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Abstract

Objective The Bipolar Youth Action Project (BYAP) is a two–year, youth–driven study. Our research explored: 1) bipolar disorder (BD) self–management strategies that are effective for Vancouver Island youth with BD; and 2) methods preferred by youth participants for sharing these strategies with their communities and support circles.

Methods The study employed a group of seven Youth Action Group members with BD who worked with the research team in a Community–Based Participatory Research (CBPR) framework. In collaboration, we designed and executed two Vancouver Island–based Research Forums, inviting youth with BD from the wider community to share their knowledge on self–management. Qualitative (focus group), consultation (World Café), and arts–based (graphic recording) methods were utilized. Qualitative findings underwent thematic analysis within a CBPR orientation.

Results Twenty-nine youth participants with BD were recruited to the two forums. Focus group findings identified five overarching themes, including ‘sources of self–management strategies.’ Half of the focus group participants described using online sources to either learn more about self–management or to strengthen their social support networks. World Café consultations indicated that, while participants primarily used online sources for mental health information, they experienced barriers, namely stigma and difficulty finding credible, safe, and evidence–informed information.

Conclusion Youth engagement in BD research and knowledge exchange is feasible. Moreover, youth with BD have constructive and important insights to share which, if harnessed, will help the research community to develop appropriate, effective, and safe online mental health spaces for future generations.

Introduction

With the exponential rise in internet use, people are increasingly searching for health–related information online.1 The internet may be a particularly valuable health communication and education tool for populations affected by stigmatized illnesses.2,3

Seeking mental health information online may be particularly attractive to people experiencing bipolar disorder (BD).4 BD, a mood disorder characterized by episodes of depression and/or mania/hypomania, affects around half a million Canadians5 and is often accompanied by diminished social support, stigma, and reduced quality of life (QoL).6,8 Onset of BD typically occurs in young adulthood. Recent research has shown that, unlike in multiple episode or ‘late stage’ BD, QoL remains relatively well preserved early in the course of the condition,9 suggesting that there is a critical window of opportunity for early intervention and support. To our knowledge, however, no research has yet explored how best to help youth with BD access online mental health information.

Youth are clearly heavy users of the internet, with 93% online regularly.10 Developing online mental health information targeted toward youth makes sense due to commonly cited barriers to help-seeking, such as low mental health literacy, concerns regarding stigma, and preferences for self–reliance.11 Yet, to our knowledge, no research has yet explored online mental health information specifically for youth living with BD.

This article presents findings from the Bipolar Youth Action Project (BYAP), which was designed to explore: 1) self–management strategies that are effective for youth on Vancouver Island who live with BD; and 2) the best methods for sharing these strategies with other youth, their families, and the wider community. Specifically, this paper shares knowledge from the BYAP project about: 1) how BYAP youth participants currently seek mental health information online, and 2) youth preferences and desires for future developments in the arena of online mental health information provision.

Materials and methods

Community-based participatory research

Acknowledging the complexities of BD research and limited multidisciplinary work in this area, we established the Collaborative RESearch Team to study psychosocial issues in BD (CREST.BD) at the University of British Columbia in 2007.12 CREST.BD includes academic researchers, healthcare providers, and community members who are dedicated to developing knowledge about psychosocial factors in BD through a Community–Based Participatory Research (CBPR) orientation.12

CBPR engages with community members with lived experience of an issue or health condition (in this instance, people living with BD and their supporters), with aims of building research capacity and influencing social change.13 CBPR is based on the premise that collaborating with those with direct involvement and knowledge about an issue under investigation yields findings of relevance to the
community. Substantial community input is sought throughout the research process.

A clear rationale can be made for the potential benefits of youth engagement in research and evaluation.14 Indeed, participatory approaches have been used successfully in various areas of youth mental health research.15,16 Recognizing a gap in the application of CBPR approaches to BD research in youth, we secured funding from the Vancouver Foundation for a two-year CBPR project to build knowledge on effective self-management in youth with BD. Integral to this process was the establishment, at study inception, of a Youth Action Group (YAG) consisting of twelve Vancouver Island–based peer researchers (aged 20 to 25) living with BD (type I, II, or not otherwise specified (NOS)), two of whom acted as co–leads of the YAG. In addition to the YAG, the project team consisted of: two lead researcher team members (EM and AP), a youth engagement expert from London, ON (EC), a graduate student trainee with experience in qualitative methods (KN), and a research coordinator (NE).

The YAG members collaborated with the wider team to design, implement, and evaluate the findings from two research forums held in Victoria, BC on July 12th and November 15th, 2015.

**Forum participants**

Forum participants were required to have a (self–reported) diagnosis of BD (type I, II, or NOS), be between 16 and 25 years, and reside primarily on Vancouver Island. Forum II participants included some of the same participants from Forum I, but participants were not required to attend both forums. Ethics approval for BYAP was granted by the University of British Columbia Behavioural Research Ethics Board (H14-00063) and the Island Health Research Ethics Board. Participants aged 19 and over provided written consent; participants aged 16 to 18 provided both their written assent and the written consent of a legal guardian. Both the YAG members and the Forum participants received honoraria for their participation.

**Table 1 | Summary of Forum I demographic and clinical characteristics**

<table>
<thead>
<tr>
<th>Gender</th>
<th>Total N</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>6 (28.0%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>14 (66.7%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1 (4.8%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Total N</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian</td>
<td>14 (66.7%)</td>
<td></td>
</tr>
<tr>
<td>Other (Ethiopian-Canadian, Polish-Canadian, Portuguese-Canadian, Canadian)</td>
<td>5 (24.0%)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>2 (9.5%)</td>
<td></td>
</tr>
</tbody>
</table>

| Age of diagnosis M (SD) | Total N | 17.3 (3.8) |

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Total N</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDI</td>
<td>5 (23.8%)</td>
<td></td>
</tr>
<tr>
<td>BDII</td>
<td>6 (28.6%)</td>
<td></td>
</tr>
<tr>
<td>BD NOS</td>
<td>7 (33.3%)</td>
<td></td>
</tr>
<tr>
<td>Unsure</td>
<td>3 (14.3%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Employment</th>
<th>Total N</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Student</td>
<td>12 (57.1%)</td>
<td></td>
</tr>
<tr>
<td>Employed</td>
<td>4 (19.0%)</td>
<td></td>
</tr>
<tr>
<td>Long-term Disability</td>
<td>1 (4.8%)</td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>3 (14.2%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1 (4.8%)</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2 | Summary of Forum II demographic and clinical characteristics**

<table>
<thead>
<tr>
<th>Gender</th>
<th>Total N</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>7 (87.5%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1 (12.5%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Total N</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian</td>
<td>4 (50.0%)</td>
<td></td>
</tr>
<tr>
<td>Other (Filipino-Canadian)</td>
<td>2 (25.0%)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>2 (25.0%)</td>
<td></td>
</tr>
</tbody>
</table>

| Age of diagnosis M (SD) | Total N | 16.6 (1.5) |

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Total N</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDI</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>BDII</td>
<td>4 (50.0%)</td>
<td></td>
</tr>
<tr>
<td>BD NOS</td>
<td>3 (37.5%)</td>
<td></td>
</tr>
<tr>
<td>Unsure</td>
<td>1 (12.5%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Employment</th>
<th>Total N</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Student</td>
<td>5 (62.5%)</td>
<td></td>
</tr>
<tr>
<td>Employed</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>Long-term Disability</td>
<td>1 (12.5%)</td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>1 (12.5%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1 (12.5%)</td>
<td></td>
</tr>
</tbody>
</table>

**Data collection**

**Forum I Focus Groups**

Forum I explored the question of “what self–management strategies are effective for youth on Vancouver Island who live with BD?” Qualitative focus groups were selected as the primary data collection method with the goal of fostering group dialogue in a safe atmosphere. An arts–based approach (graphic recording) was also incorporated. Focus groups (n=5) were semi–structured (see Table 3 for details of focus group questions), 90 minutes in length, and facilitated by an (adult) team member with experience in qualitative methods and a YAG member taking notes. Focus group proceedings were audio recorded and then transcribed verbatim by YAG co–lead LL.

**Forum II World Café**

Forum II explored the question of “what are the best methods for sharing information on self–management strategies with other youth, their families, and the wider community?” The event began with YAG members sharing the knowledge gained in Forum I through presentations, group activities, and arts–based methods. A World Café approach was selected as the primary data collection method for Forum II. World Café involves inviting participants to circulate among several tables, each table with its own host who facilitates a different discussion topic. Participants bring questions or thoughts from previous tables to new ones, allowing for cross–pollination of ideas from which themes may emerge.17 Forum II World Café tables (n=4) were each devoted to a different medium for sharing self–management information: 1) written, 2) in–person, 3) visual, and 4) social media. Questions posed for each table were: “What media appeal to you?”, “What is and isn’t effective about those?”, and “How would you use those to effectively target youth with BD?” Forum participants moved between tables for 20 minute discussions hosted by a research team member with experience in group facilitation. YAG members also participated in the World Café. World Café discussions were recorded and analyzed by LL and research coordinator NE.

**Forum I analysis**

Focus group findings were analyzed using thematic analysis.18 LL initially reviewed the transcripts for pattern and structure before inductively coding them.19 The inductive codes were organized into categories, forming the initial coding framework. LL then re–analyzed 25% of the data. LL and KL regularly discussed the coding framework (e.g. during uncertainty around the definition or organization of a code), leading to ongoing refinement of the framework and subsequent themes. As the framework evolved, LL co–analyzed a total of 50% of the data to
ensure internal consistency and analytic validity. The findings presented in this paper are supported by direct quotes from participants to enable readers to evaluate the interpretations. All identifiers have been removed or changed to ensure confidentiality.

**Forum II analysis**

World Café group discussions were audio recorded and subsequently analyzed by LL and NE. Concrete ways of information sharing discussed by each group were extracted and organized according to the World Café questions posed: 1) written Media, 2) in-person methods, 3) visual media, 4) social media.

**Results**

**Participant characteristics**

Forum I recruited 21 participants: fourteen who identified as female, six as male, and one as gender neutral. All participants self-reported as having a diagnosis of BD I, II, or NOS. 3 participants reported having received a diagnosis of BD, though were unsure of their specific diagnostic category. Forum II recruited eight participants; all identified as female except one individual who identified as gender neutral. Diagnostic breakdown by gender for both forums was BD I: 4 females, 2 males; BD II: 1 other gender, 9 females, 0 males; NOS: 6 females, 3 males; unsure of specific BD diagnosis: 3 females, 1 male. All participants from both Forums, except three individuals, resided in Victoria. Full demographic and clinical characteristics of participants are provided in Tables 1 and 2.

**Forum I focus group results**

Thematic analysis identified five primary themes: 1) healthy lifestyles help regulate mood in youth with BD; 2) in-the-moment strategies to manage depressive and manic mood states; 3) support networks are helpful; 4) sources of self-management strategies; and 5) key messages we want to share.

Within the ‘sources of self-management strategies’ theme, many focus group participants described the process of identifying self-management information as being largely trial and error. Participants proactively expended significant time and energy searching for strategies that work for them. They described exploring diverse sources for BD information, including books, online resources, healthcare professionals, and peers. 10 of the 21 focus group participants (47%) described accessing online information about self-management of BD, specifically through Facebook, Reddit, YouTube and online videos, websites, apps, and Tumblr.

Participants described using online sources primarily to 1) learn more about self-management strategies for BD (Table 4-1) or to 2) strengthen social support networks (Table 4-2). Apps that monitored mood states and informed personalized self-care (DO-158), as well as apps designed to target mood symptoms (CB 239), were used to learn more about self-management strategies for BD. Strengthening social support networks was seen as valuable in particular by participants who had few, if any, peers with BD (EL D315-317). For example, participants cited using Reddit to find online “bipolar pen pals” (GD 334). Online sources were also used to improve off-line support networks.

Stigma and misinformation were also key points brought up by focus group participants. Many struggled with mental health stigma, feeling afraid to disclose their condition at school or to their friends, feeling shame about a new diagnosis, or feeling that their friends and family were misinformed about BD. Although most participants were judicious about disclosure, many indicated that directing members of their support networks to credible online mental health information helped to spread understanding and awareness of mental illness within their social circles (MI B94) and to decrease stigma and misinformation in the context of their own lives. Importantly, some participants also cited that their ability to share online content with their networks and to interact with peers online not only improved their existing relationships (MI B34), but also gave them a feeling of increased empowerment and control over their lives (DS A223, MI B117-121).

**Forum II World Café results**

Across all four World Café table discussions, participants cited the internet as the primary vehicle they used for accessing mental health information. When asked about what participants wanted from online health information, feedback centered on existing barriers to accessing information online. The main barriers described were stigma in online environments, negative or distressing content, and difficulty finding credible content.

Stigma was a significant barrier to accessing mental health information online. Participants described fears of being judged for what they posted, shared, or even viewed online, particularly with regards to Facebook. Many participants mentioned having contacts on Facebook who were not aware of their mental illness and felt dissuaded to share mental health information for fear of “ outing” themselves as living with a mental health condition.

With regards to online platforms that allow for more anonymity (e.g Reddit), participants expressed that the freedom of being “faceless” can itself create room for stigma and negative/distressing content. Interestingly, some participants reported negative content as a worse problem on user-driven platforms that include more discussion about mental health conditions, such as Reddit and Tumblr. Some participants described how Reddit members would distort the discussion about mental health conditions, such as Reddit and Tumblr. Participants described how Reddit members would distort the discussion about mental health conditions, such as Reddit and Tumblr. Participants described how Reddit members would distort the discussion about mental health conditions, such as Reddit and Tumblr. Participants described how Reddit members would distort the discussion about mental health conditions, such as Reddit and Tumblr. Participants described how Reddit members would distort the discussion about mental health conditions, such as Reddit and Tumblr.

Finding credible, high-quality online content was also a significant barrier. Many participants expressed that they, and those in their support networks, had often resorted to “Doctor Google,” that is, relying on indiscriminate Google searches to find mental health self-management information. Participants noted that it was difficult for them to know where to look for such information; as such, they and their supports used information that they later found to be inaccurate. A desire for credible, centralized, safe, and stigma-free online content was the dominant request.

**Discussion**

The emerging field of online mental health information provision for youth with BD offers both promise and potential pitfalls. In terms of promise, prior research suggests that many people with BD are attracted to the accessibility and anonymity of online spaces, which can foster peer-provision of emotional support on complex issues, such as stigma, isolation, disclosure, and interpersonal relationships. Research has also highlighted the potential benefits of online sources for those recently diagnosed with BD, in an effort to support the development of self-management strategies, peer connections, and acceptance of BD. In terms of pitfalls, however, existing online BD resources are heterogeneous in content quality, and privacy and security issues abound. The sheer diversity of currently available online
resources and interventions for BD hampers drawing conclusions about their collective efficacy.\textsuperscript{20} Clear gaps are also apparent, for example, few available BD online tools address QoL or recovery–focused orientations.\textsuperscript{24}

### Table 4 | Forum 1 focus group quotes

<table>
<thead>
<tr>
<th>1</th>
<th>Learning about self-management strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td>“...[on Tumblr] people send master posts, of like, links... ‘If you’re feeling this, go to this website,’ and it’ll... give you ideas of things to do. And, so... that’s where I... started to learn about [self-management].” (MI-B133/136)</td>
<td></td>
</tr>
<tr>
<td>“I know there’s some really good apps that you can download that... you know, it’ll remind you every hour, like, ‘how are you feeling right now?’ And you can kind of track, like... maybe I noticed that, you know, I didn’t go to bed ‘til three last night, and so I had a really crappy day the next day, or something like that. And you can kinda start making connections and form your own self-care plan, and realize that, say I have to go to bed by ten every night, or whatever.” (DO-158)</td>
<td></td>
</tr>
<tr>
<td>“I go on Tumblr a lot, and there’s a lot of like posts, about like, self-care...” (MI-B133/136)</td>
<td></td>
</tr>
<tr>
<td>“There’s an app called ‘What’s Up’ that really helps me out. It’ll ask you, ‘...name five things you see,’ or ‘name five things you smell.’ And it actually snaps me out of my mood sometimes. There’s like, lots of little mini games on it and whatever... I use it weekly.” (CB-239)</td>
<td></td>
</tr>
<tr>
<td>“I watched a lot of videos on YouTube about [self-management]. And that helped.” (CB-C370)</td>
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<table>
<thead>
<tr>
<th>2</th>
<th>Strengthening social support networks</th>
</tr>
</thead>
<tbody>
<tr>
<td>“I find there are some pretty great forums... that you can, even if you’re not aware of many people around your area, that can give you support and share their perspective” (EL D315-317)</td>
<td></td>
</tr>
<tr>
<td>“I actually went out and found a couple of bipolar pen pals online... so I have more people to talk to. I found them through Reddit.”</td>
<td></td>
</tr>
<tr>
<td>“We love Reddit!” [laughter] (G-D334)</td>
<td></td>
</tr>
<tr>
<td>“Just connecting with other people... it really helps you feel like you’re not alone... Cause I’m, like, someone newly diagnosed, I feel like, ‘Oh, this is... my life from now on!’ But then, seeing someone else [living well with BD], it’s like, ‘no, this is not how it’s gonna be every day... you’ll eventually figure it out, and... everything will make sense.” (MI B117-121)</td>
<td></td>
</tr>
<tr>
<td>“When I’m depressed, I go into, like, hermit mode. I will just shut off from... everything. And so, even though it’s hard, I find like, reaching out to friends... on Facebook [is easy], ‘cause you’re not doing [it] face-to-face, you’re... a little bit detached. So it’s easy to say, you know, ‘Hey, I’m not feeling so well, you know, can you come over.’... Even if they just, like, message you [and say], ‘How are you, hi.’ That can... help brighten your day.” (MI B34)</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>3</th>
<th>Challenging stigma</th>
</tr>
</thead>
<tbody>
<tr>
<td>“I think the education is such an important part. Like... I send links to my mom all the time.” (MI B94)</td>
<td></td>
</tr>
<tr>
<td>“I’ll just send her links, uh, pages, articles I see, and get her to read them. And she’s more... educated about it.”</td>
<td></td>
</tr>
<tr>
<td>“Yeah, I do that as well, and same with my friends. That’s how I educate them.” (MI B94)</td>
<td></td>
</tr>
<tr>
<td>“It was a really big thing for me to teach my mom... about my mental illness, so that she can better help me. And she’s willing to learn.” (ME B78)</td>
<td></td>
</tr>
<tr>
<td>“[Having respectful supporters gives] some level of control over my own life. [It’s important that I’m] Not... being treated like a child.” (DS A223)</td>
<td></td>
</tr>
</tbody>
</table>

This project applied a CBPR approach to build knowledge on how youth with BD are currently using online self–management resources and their recommendations for future developments. Focus group findings from Forum I indicated that participants accessed online spaces primarily to learn more about self–management strategies and to strengthen their social support networks. Forum II consultations indicated that youth encountered significant barriers when accessing self–management information online, including stigmatizing attitudes, negative or distressing content, and difficulties finding credible content. These results reflect observations from the wider literature on the use of online health information by youth facing mental health challenges. For example, prior research has shown that youth commonly search online for information not just on symptoms and diagnoses, but also self–management strategies and interpersonal issues.\textsuperscript{25} Approximately half of youth with mental health issues report using forums to connect with peers.\textsuperscript{25,26}

Of interest is our finding that BYAP project participants were often hesitant to use more public social media platforms, such as Facebook, for mental health support, describing fears of stigmatization. Prior research in this area yields mixed statistics. One survey, for example, reported 77% of youth were unlikely to use social media platforms to access mental health information,\textsuperscript{27} whilst another survey on the use of specific social media platforms reported high rates of usage for more anonymous platforms, such as YouTube (85%), with less use of less private platforms, such as Facebook (58%), Skype (40%), and Twitter (39%).\textsuperscript{27} Social media platforms that protect privacy and identity might, therefore, be preferable moving forward.

Our findings that youth who live with BD face barriers in sourcing credible health resources online and their desire for centralized sources of online health information are in line with findings from previous studies.\textsuperscript{28,29} Prior research has identified that youth report feeling uncomfortable conducting online searches for mental health information, both in terms of their own abilities to perform internet searches, as well as the way health information is presented online.\textsuperscript{27} Finally, previous studies have found that youth required a tailored mix of online and in–person mental health supports,\textsuperscript{30} which is a finding echoed here.

In an effort to provide a ‘one stop shop’ for evidence–based information on self–management of BD, CREST.BD recently designed, developed, and piloted a sophisticated online ‘Bipolar Wellness Centre.’ A range of engagement strategies are embedded within the website, including webinars that speak to fourteen diverse areas of BD self–management, videos where a peer–researcher with BD illustrates concrete examples of self–management in action, and a ‘Living Library’ where users can ‘check out’ an expert with lived experience of BD via secure telehealth software to help tailor self–management resources to their specific context. Serving as a ‘gateway’ to the Bipolar Wellness Centre is an online QoL Tool measurement system, which empowers users to access tailored self–management evidence and resources based on their personal QoL profile. Many features of the Bipolar Wellness Centre complement the priorities of youth for online health information, for example, it is credible, centralized, and built around messages of hope and recovery by prioritizing language and content that are empowering rather than stigmatizing. However, the website was designed initially for adult knowledge users; we look forward to incorporating the results from the BYAP project into the website moving forward and creating youth–friendly content.
There are potential limitations to our research that warrant consideration. First, our YAG had no visible minority members and only 14% (n=4) of total forum participants self-identified as visible minorities; consequently, discussions were not held on the topic of mental health and racial marginalization. Second, conversations around sexual orientation and the needs of LGBTQ youth were also missing from both forums. The lack of voices from these populations greatly impeded our ability to apply an intersectional lens to the provision of tailored, appropriate online mental health information. Third, with all but three participants residing in suburban areas, generalizability to both rural and urban populations is limited. Finally, it is important to note that none of our participants or YAG members self-identified as of First Nations descent, although our research was conducted on the traditional territories of the Songhees and Esquimalt First Nations.

Notwithstanding the above limitations, the results of our community-engaged project incrementally advance this nascent field of research.

Conclusion

Our team applied a CBPR approach to develop knowledge on the self-management strategies deemed effective by Vancouver Island youth living with BD and their preferred methods for sharing information about these strategies with the wider community. Focus group findings spoke to five central themes: 1) healthy lifestyles help regulate mood in youth with BD; 2) in-the-moment strategies to manage depressive and manic mood states; 3) support networks are helpful; 4) sources of self-management strategies; and 5) key messages we want to share. While youth with BD primarily access online sources for mental health information, they often experienced significant barriers in this process, including stigma and difficulty finding credible, safe, and evidence-informed information. At a broad level, our results demonstrate that youth engagement in BD research and knowledge exchange is feasible. More significantly, they show that youth with BD have constructive and important insights to share which, if harnessed, will help us develop appropriate, effective, and safe online mental health spaces for future generations.

References


Resolution of acquired von Willebrand Syndrome secondary to hypertrophic obstructive cardiomyopathy following septal myectomy

Johnathan Hoggarth; Harry Rakowski, MD; Erik Yeo, MD; Anthony Ralph-Edwards, MD

Citation: UBCMJ. 2016: 8.1 (32-33)

Abstract

We report the case of a 69–year–old Caucasian male patient with hypertrophic obstructive cardiomyopathy, severe gastrointestinal bleeding, and acquired von Willebrand Syndrome. The patient had previously been known to have hypertension, hyperlipidemia, and a family history of early atherosclerosis. Pre–operative blood tests showed normal von Willebrand factor activity with a decrease in high molecular weight multimers. Septal myectomy was performed in treatment of his hypertrophic disease. Follow–up blood tests indicated normal von Willebrand factor activity and high molecular weight multimer levels. Gastrointestinal bleeding has not recurred following surgery. In conclusion, septal myectomy resolves von Willebrand syndrome secondary to hypertrophic obstructive cardiomyopathy, in this case. As von Willebrand factor multimer testing can be used for the diagnosis of acquired von Willebrand syndrome, it should be considered in patients who have gastrointestinal bleeding coinciding with hypertrophic obstructive cardiomyopathy.

Background

Von Willebrand Syndrome (vWS) is defined as a deficiency of the blood protein von Willebrand factor (vWF) that can result in excessive bleeding. It can be inherited and, in rare cases, acquired vWS can develop later in life secondary to many conditions such as autoimmune and congenital and acquired cardiac diseases. While there is no cure for inherited vWS there are several treatment options that help supplement vWF. In acquired cardiac cases, repair of jet lesions will result in normalization of vWF. In patients who have been investigated for severe bleeding and who have been found to have vWS, it would not be unreasonable to screen for cardiac lesions with echocardiography.

In 1958, Dr. Heyde first described an association between gastrointestinal (GI) bleeding and aortic stenosis. Heyde’s syndrome, as it is now known, has been linked to the development of acquired vWS. High shear stress, brought on by aortic stenosis, was subsequently shown to cause the proteolysis of high molecular weight multimers (HMWM) of vWF. This deficiency in HMWM causes acquired vWS and leads to the GI bleeding as described in Heyde's Syndrome. Recently, it has been indicated that hypertrophic obstructive cardiomyopathy (HOCM) can also lead to a decrease in vWF through an analogous mechanism to aortic stenosis in Heyde's syndrome.

Here, we describe a patient diagnosed with HOCM and acquired vWS who had a decrease of HMWM.

Case

A 69–year–old man was seen in the Toronto General Hospital (TGH) cardiac clinic with New York Heart Association and Canadian Cardiovascular Society class III symptoms of shortness of breath and angina. Beginning in 2009, the patient was found to be anemic and, over the next four years was transfused a total of 119 units of blood. The year prior to cardiac referral, he was found to have bleeding small bowel angiodysplasia as the cause of his blood loss following upper and lower endoscopy. This was definitively treated with endoscopic sclerotherapy. In the process of the patient's GI bleeding investigations he was also diagnosed with HOCM and coronary artery disease. Over the intervening year, the patient’s cardiac symptoms progressed precipitating a referral. The patient's coronary risk factors included hypertension, hyperlipidemia, and a family history of early atherosclerosis. His medications, at the time of assessment, consisted of acetylsalicylic acid, metoprolol, atorvastatin, and disopyramide. Prior to endoscopic treatment, 1-3 units of blood each week were necessary to maintain acceptable hemoglobin levels. At the time of presentation to TGH, a cardiac workup demonstrated significant left ventricular outflow tract obstruction associated with typical findings of HOCM. On review of this patient’s echocardiogram, his basal septum measured 27 mm in maximal thickness (normal 8-12 mm). A left ventricular outflow obstruction gradient was measured at 53-63 mmHg, which increased to 86 mmHg with Valsalva maneuver. A left ventricular outflow track gradient of less than 20 mmHg is considered normal and should not increase with Valsalva maneuver. Posteriorly directed mitral regurgitation was also visualized. A coronary angiogram demonstrated significant two–vessel coronary disease. Based on his symptom status, the patient was considered for myectomy surgery. Pre–operative blood work indicated the patient had vWF well within normal range, finding the vWF antigen to be 120 units/mL and activity to be 107 units/mL. Multimer studies showed absent or markedly decreased HMWM without the increase in low molecular weight multimers that would indicate acquired vWS.

Over the course of the investigation, the patient was diagnosed with Heyde’s syndrome. This is normally described in patients with severe aortic stenosis where, presumably, the shear stress of blood going through the aortic valve causes an acquired form of vWS with recurrent bleeding. In those patients, aortic valve replacement often leads to resolution of the vWS.

The patient was admitted to hospital for septal myectomy and aorto–coronary bypass grafting. During surgery, the myectomy was performed, spanning the mid portion of the right coronary cusp...
to the lateral border of the mitral valve annulus. The specimen was approximately 15 mm in thickness and carried nearly 40 mm into the ventricle. A wedge of ascending aorta approximately 1.5 cm in length was excised anteriorly. Following the myectomy, saphenous vein grafts were constructed to the diagonal and distal right coronary arteries.

Ten months after surgery, the patient had no symptoms of angina or shortness of breath. He had not experienced any bleeding since the surgery. A follow-up vWF profile, performed at nine months post-surgery, found vWF antigen was 144 units/mL, with activity at 133 units/mL; both are within the normal range. The follow-up multimer test showed normal HMWM levels following surgery. Both HMWM, as well as intermediate weight multimers, were present at normal levels. This indicates normal vWF function and resolution of vWS.

**Discussion**

Septal myectomy for HOCM, resulting in resolution of left ventricular outflow tract obstruction, normalized the HMWM level in a patient with severe GI bleeding and acquired vWS. There is a documented link between HOCM and acquired vWS. It has been previously determined that shear stress brought on by high velocity restrictive lesions such as aortic stenosis, ventricular septal defect, and patent ductus arteriosus can cause the proteolysis of HMWM. High amounts of shear stress, brought on by HOCM, can cause the proteolysis of HMWM. The turbulence and flow restrictions caused by HOCM have also been shown to cause a reduction in HMWM. This case supports the theory that HOCM causes the proteolysis of HMWM. The HMWM loss present prior to surgery normalized after cardiac repair. We propose the decreased shear stress after septal myectomy resolved the severe GI bleeding caused by acquired vWS secondary to HOCM. Therefore, patients diagnosed with HOCM who experience severe GI bleeding should be considered as possibly having acquired vWS and pre-operative vWF multimer testing may be of benefit. While there is other evidence of HOCM leading to acquired vWS, there is still a lack of knowledge regarding the correct protocol to follow. This case study hopes to further indicate proper procedures when presented with patients with HOCM and severe GI bleeding.

**References**

Could anticoagulation with Rivaroxaban have precipitated a spinal epidural hematoma: From independent mobility to paraplegia

Gautam Sarwal, MD; Charlotte Dandurand, MD; Agnes Y. Y. Lee, MD, FRCPC; Viet H. Vu, DO, ABPMR

Abstract
A 81 year-old male, with atrial fibrillation and a bovine prosthetic valve on aspirin and rivaroxaban, presented with acute back pain, limb weakness and paraplegia within six hours. Urgent spine magnetic resonance imaging showed a massive epidural bleed from T1 to T12. A spontaneous spinal epidural hematoma (SSEH) was diagnosed. The exact etiology remains unclear, however, it was believed to have been secondary to the patient’s underlying hypertension and modest hypocoagulation. Urgent decompression offers the best probability of neurologic recovery, however, the patient was not a surgical candidate as the cord had infarcted and the risk of a fatal intra–operative bleed was high. He was ultimately transferred for rehabilitation on aspirin. His spinal cord injury was graded as T10 American Spinal Injury Association (ASIA) Grade B. Anticoagulation was never restarted and the patient received an atrial appendage closure to reduce the risk of clot formation. To our knowledge, this is the first report of a long segment SSEH and adverse reaction to rivaroxaban with unusually rapid and permanent neurologic sequelae.

Background
Spontaneous spinal epidural hematomas (SSEH) were first described by Jackson in 1869.1 It is rare and estimated in incidence at 0.1 per 100,000 people, but carries devastating neurological morbidity.2-4 A spontaneous bleed is defined as one not associated with lumbar puncture, spinal anaesthesia, blunt force trauma, blood dyscrasias, vascular malformations, or tumours.2,5-8 SSEH should be suspected in any anticoagulated patient who presents with new onset back pain associated with paraparesis, altered sensation, or bowel and bladder dysfunction.2,9,10

Urgent spinal MRI remains the gold standard in localizing and examining the craniocaudal extension of the hematoma as well as demonstrating the compressive effects on the cord.11-13 Early decompressive laminectomy and hematoma evacuation remain most effective at preventing permanent neurological sequelae if performed within twelve hours from the onset of symptoms related to cord compression.14-17

We present our case for several reasons. Despite a typical presentation and rapid neurosurgical workup under eight hours, the patient suffered an extensive bleed and concomitant cord infarct, making him a poor candidate for successful surgery. Therefore, SSEH has the potential for rapid and permanent neurologic compromise despite attempts at prompt decompression. Such a case has not been reported with rivaroxaban. To our knowledge, only a single case of SSEH with ibuprofen and rivaroxaban has been presented where conversely, the patient made a complete and spontaneous recovery.18 Second, our case poses a dilemma on whether to resume antithrombotic therapy. Discontinuing therapy increases the risk of a cardioembolic stroke, whereas restarting it raises the possibility of a recurrent bleed.

Case presentation
An 81 year-old male with a history of paroxysmal atrial fibrillation (AF) (CHADS2 score 4) and a bovine aortic valve on rivaroxaban (Xarelto) 20mg daily and low–dose aspirin, presented with sudden onset, sharp mid–thoracic back pain that started while at rest. There was no history of recent surgery, spinal anaesthesia, or trauma. He was previously mobilizing and functionally independent. His past medical history included hypertension, hyperlipidemia, and a history of multiple transient ischemic attacks. He was initially treated with low–dose aspirin and warfarin from 2002 until August 2014, when he was changed to rivaroxaban because of labile International Normalized Ratio (INR) values.

On presentation to the Emergency Room, he complained of excruciating back pain and bilateral lower extremity paraparesis, but was able to demonstrate a non–antalgic gait. Six hours later, while awaiting investigations, the patient lost all motor function in his lower extremities and noted no sensation to light touch or painful stimuli below his waist.

On examination, the patient was alert and oriented with a blood pressure of 155/65 and a pulse of 90 bpm and regular. There was no blood pressure asymmetry between the upper limbs. He had a normal head, neck, cardiovascular, and abdominal physical exam. A neurological exam revealed complete loss of sensation and flaccid paralysis below T10 bilaterally. There was no spasticity, clonus, or Babinski reflex at the toes. Rectal tone and a bulbocavernous reflex were absent.

Investigations
The INR was elevated at 1.7, but the platelet count and activated partial thromboplastin time (aPTT) were normal. Renal function was also preserved. Thrombin time was not measured.

Spinal MRI and a computed tomography (CT) scan revealed an extensive long segment hyperacute dorsal epidural hematoma that extended from T1 to T12 (Figure 1). Cord compression was diffuse but worst at the T9 T10 level. The hematoma measured 10x15 mm at its maximum extent in cross section. There was no dural arteriovenous (AV) fistula or vascular malformation noted.
Outcome and follow-up

Thoracic spinal CT scans performed two and four weeks after the patient's initial presentation showed no further bleeding and no new abnormalities to suggest a previously missed vascular malformation or AV fistula. Low-dose aspirin was restarted two weeks after without recurrence of symptoms. A month later, he regained scant sensation in the sacral region but had not gained any sensory or motor function in his lower extremities. Accordingly, his injury was graded a T10 American Spinal Injury Association (ASIA) grade B injury, and the patient transferred for inpatient rehabilitation. He also remained incontinent of both bowel and bladder function, and as such, he continues to receive intermittent urinary catheterization and bowel care to manage these routines.

Given his neurologic deficits, he was engaged in physiotherapy aimed at improving his functional independence with transfers and wheelchair mobility.

Restarting anticoagulation, however, posed a dilemma. Off anticoagulation, he faced a 5% per year risk of a cardioembolic stroke, whereas restarting anticoagulation increased the possibility of a recurrent bleed. Ultimately, the patient received a percutaneous left atrial appendage closure device to reduce the risk of clot formation.

Discussion

In the background of anticoagulation, though rare, a SSEH should be considered in cases of sudden onset back pain with symptoms of spinal cord compression. It represents 40% of all spinal epidural bleeds, whereas anticoagulation therapy accounts for 17% of such cases. The exact cause remains unknown. The literature cites an association with the use of anticoagulants, antiplatelet therapy, thrombolysis, hypertension, or a coagulopathy such as haemophilia or leukemia. In our patient, the combined antiplatelet effect of aspirin and Factor Xa inhibition by rivaroxaban likely contributed to modest hypocoagulation. With a concomitant history of hypertension, the cause was likely multifactorial.

Non-steroidal anti-inflammatory drugs such as aspirin often cause a transient but modest increase in bleeding time. Typically, this does not exceed the reference limits unless combined with an anticoagulant. It does not, however, explain the INR at 1.7. This was likely secondary to rivaroxaban, as the patient denied using warfarin for over three months. Rivaroxaban has been shown to be effective in non-valvular AF, as evaluated in the ROCKET trial (Rivaroxaban–once daily, Oral, direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation). The incidence of major bleeding was found to be comparable between rivaroxaban and warfarin at 3.6% and 3.4% respectively. Major bleeding included intracranial and spinal bleeds, amongst others. With the addition of aspirin, we expect the risk of major bleeding to be increased. Smith et al. have reported that routine coagulation assays like the INR and aPTT are ineffective at determining the presence and concentration of novel anticoagulants, including rivaroxaban. They often test normal, and elevated levels may be consistent with supratherapeutic concentrations. As such, it would have been difficult to acutely determine the patient's anticoagulation status. He was likely excessively anticoagulated, given the elevated INR and concurrent aspirin use. However, our patient had valvular AF, and we were unable to find literature supporting the use of rivaroxaban. He had been started on this agent in the community due to labile INR values, albeit warfarin remains the

Differential diagnosis

The differential diagnosis included a spinal abscess, tumour, transverse myelitis, and an acute disc herniation. However, the above findings and radiological evidence were consistent with an atraumatic SSEH on dual antithrombotic therapy, which as previously reported, is rare.

Treatment

SSEH is a neurosurgical emergency, and early decompressive laminectomy and hematoma evacuation remain the treatment of choice. Non-surgical treatment is only valid if the neurologic deficits resolve spontaneously soon after onset or in cases without neurological deficits or cases with advanced and irreversible spinal cord injury.

Given our patient's neurologic deficits and above findings, it was felt the spinal cord had already infarcted, making him a poor candidate for successful surgery. Due to the lack of an antidote to rivaroxaban, the patient remained anticoagulated, which increased his risk of a fatal intra-operative bleed. Accordingly, non-surgical management was recommended and further anticoagulation was held, including deep vein thrombosis prophylaxis.

Figure 1 | Sagittal T2 weighted MRI image demonstrating an extensive epidural hematoma extending from T1 to T12 spinal level.
agent of choice in patients with valvular AF.

The most common site of an epidural spinal hemorrhage is the thoracic spine, which was evident in our patient.33 The bleeding is believed to originate from the epidural venous plexus.6,22 This explains why the majority of all epidural hematomas are located posterior to the cord, which is in the vicinity of the venous plexus, as seen in our case.20 This network of weakened veins or “locus minoris resistentiae” can rupture on sudden increases in thoracic or abdominal pressure.6,22 Our patient was at rest during the onset of symptoms and as such, we do not believe this was a contributory factor.

SSEH has been shown in nearly all age groups but is predominantly seen in patients between 55 and 70 years of age.21 This is likely because such patients are often on an anticoagulant medication or suffer from hypertension, all of which are recognized as precipitants of SSEH. The gender ratio (male:female) is 1.4:1.10 The best choice for imaging is an urgent spine MRI, because it is non—invasive and able to localize and measure the longitudinal extension of the hematoma as well as demonstrate cord compression and signal changes characteristic of cord infarction.11,13 The age of the hematoma can also be determined because the signal intensity changes over time.33 Early MRI images appear isointense or hypointense to T1—weighted images and hyperintense on T2—weighted images.35 Most importantly, an MRI can distinguish SSEH from a differential that includes a spinal neoplasm, abscess, acute disc herniation, and transverse myelitis, while identifying underlying vascular anomalies like AV malformations, vertebral hemangiomas, or hemorrhagic tumours that may cause an epidural bleed.32 MRI imaging performed on our patient demonstrated a hyperacute spinal epidural hematoma, thus confirming the diagnosis. It helped with treatment planning because the patient was found to be a poor operative candidate given evidence of global cord infarction secondary to compression from the hematoma. It also ruled out an underlying vascular anomaly that may have triggered the SSEH. Repeat CT scans confirmed no new vascular abnormalities that may have been overlooked on the original MRI.

The most common clinical symptom of an epidural spinal hematoma is a sharp, knife—like pain at the level of the bleed, followed by altered sensation and paralysis below the affected level due to compression of the spinal roots and cord.34,35 Complete sensorimotor loss including a flaccid muscle tone, saddle anaesthesia, and loss of rectal tone suggest cord infarction, all of which signify irreversible cord injury. These findings were evident in our patient, making him a poor candidate for surgery. Consequently, he was treated conservatively. Apart from this indication, non—surgical management can only be considered if the neurologic deficits resolve spontaneously soon after onset or in cases without neurological deficits.

The treatment for SSEH is reversal of anticoagulation and an urgent decompressive laminectomy and hematoma evacuation. The neurologic recovery varies with the severity of the preoperative deficit and the operative interval.34,36 In a study by Foo et al., 45% of patients with complete neurological deficit returned to baseline function after surgery versus 95% who had incomplete deficits.33 Preoperative cord infarction was not present in either of these patients. A review by Liu et al. reported that a long segment hematoma predicted a poorer prognosis as well.38 Finally, the possibility of complete neurologic recovery was greatest if surgery was performed within 12 hours from presentation.35,36 Therefore, despite a rapid surgical workup under eight hours, the severity of cord compression from the extensive hematoma and resultant cord infarct rendered an extremely poor prognosis for successful decompression. Consequently, the patient was managed non—surgically.

In rivaroxaban trials, spinal hematomas were not encountered.39 Prior to our case, Jaeger et al. reported a patient who developed a SSEH while on ibuprofen and rivaroxaban.18 Once again, there was no clear etiology, but it was attributed to a combination of factors, including dual antithrombotic therapy and a sudden increase in abdominal pressure secondary to straining. The patient, however, recovered spontaneously while enroute for surgery. Spontaneous resolution was believed to have been caused by leakage through the intervertebral foramina or craniocaudal extension of the hematoma within the spinal canal, thus alleviating cord compression.18

Unfortunately, there are no recommendations in the literature for the prevention of SSEH because many of the reported cases were anticoagulated in the therapeutic range. With the increasing prevalence of polypharmacy, the risk of combined antiplatelet and anticoagulation therapy warrants a raised awareness. Further studies are needed to explore their effects on precipitating SSEH. More importantly, physicians should be aware of the possibility of a SSEH when sudden, unexplained back pain occurs in anticoagulated patients.

**Patient’s perspective**

I used to go on walks daily with my wife and 5—6 other seniors to the mall. That was my routine. Now I guess that will never happen again. My legs do not work, and I cannot feel anything below my waist. The worst part of this entire experience is that, despite having seen so many doctors and surgeons, no one can tell me exactly what caused this and what I did to bring this on. I am scared to think what will happen the next time I feel back pain, that is, if I’ll have any sensation to begin with.

My memory is bad enough, and now I have to remember my ‘routines’ because I cannot use the bathroom like I used to. I literally have appointments with my nurse to help me with my stool and urinary catheters, because apparently there have been times I have been sitting in my own pee.

I celebrated my first birthday with this condition on Feb 20th while in bed surrounded by my family and grandchildren. The children kept poking at all the plastic tubes and blue pads and sheets I had around me. It was a bad day for me, as my knees kept jumping up every time they poked at my legs. But they are just children.

I cannot remember what I wanted on my last birthday. It was probably unimportant. On Feb 20th, I just wished I did not have an accident in front of my family.

I don’t know if this paper will ever help me recover, but I just want my message to any doctor reading this be heard; please tell your patient of ALL side effects, no matter their age, and do not simply hand us a pamphlet on it.

**Learning Points**

- SSEH is rare, idiopathic, and requires an urgent spinal MRI followed by decompressive surgery to facilitate neurological recovery.
- Decompression performed within twelve hours gives SSEH patients the best probability of neurologic recovery.
Factors predicting recovery after SSEH include the preoperative neurological status and the operative interval.

Conservative management is only recommended if the neurologic deficits resolve spontaneously after onset, in cases without neurological deficits, or in cases with advanced and irreversible spinal cord injury.

SSEH should be suspected in patients on anticoagulants who present with new onset back pain and symptoms of cord compression, especially those on dual antithrombotic agents.

References

The resurrection of psychedelic psychiatry and its role in addiction treatment

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Abstract
Psychedelic psychiatry, a field which was previously popular in the 1950’s to 1970’s, has received renewed interest as an increasing number of recent studies have highlighted the potential role of hallucinogens in treating addictions and various mental illnesses. This paper looks at evidence supporting the use of lysergic diethylamide, ibogaine and ayahuasca in addictions treatment and discusses the barriers that limit further exploration of the therapeutic potential of these and other psychedelic substances.

There is a long history to psychedelic psychiatry, a field that developed following the accidental discovery of lysergic acid diethylamide (LSD) in 1938.1 It has recently received a renewed interest as an increasing number of studies have highlighted the potential role of hallucinogenic substances in treating various psychiatric conditions, including addictions.2 Despite an initial surge in interest, the use of psychedelics for medical purposes in recent decades has been subject to scrutiny given the rising popularity of recreational hallucinogen use and uncertainties regarding the validity of initial studies.3 Research was further hindered by unethical applications of these substances in certain scenarios, including administration of hallucinogens to unwitting patients as part of military and intelligence agency related research. The violation of human rights in such circumstances exemplified the potential for hallucinogen use to exacerbate the power differential between physicians and patients.4 However, new studies are laying the groundwork for future research thereby proving that ethical and scientific study of these substances is not only possible but also promising. By strategically administering the substances with informed consent and in a supervised, controlled environment, researchers have been able to safely elucidate some of the psychological benefits that can be obtained from the controlled ingestion of psychedelics and confirm their valuable therapeutic role.5

Most of the initial formal data on the therapeutic effects of psychedelics stem from research conducted between 1950 and 1970.6 During this time, one of the most extensively studied psychedelics for the purpose of treating addiction was LSD.6 Dr. Humphry Osmond, a psychiatrist from Saskatchewan, along with other researchers, conducted numerous experiments with LSD and found a promising role for LSD in treating alcohol addiction.6,10 The effect was speculated to be a result of the drug’s unique ability to produce so-called “awakenings” or highly spiritual experiences in individuals taking the agent.6 Unfortunately, negative attitudes towards LSD, in large part fueled by rising popularity in recreational LSD use, led to prohibition of further trials. More recently however, a retrospective meta-analysis of studies conducted during this time showed an overall decrease in relapse rates, significant up to 6 months post-treatment in individuals treated with a single dose of LSD compared to control subjects.12

Various plant-derived hallucinogens have been used by cultures around the globe for centuries. Ibogaine, an alkaloid, is an example of one such plant compound that has longstanding traditional use in several West African tribes.13 Both clinical and laboratory studies have suggested that this drug has a promising role in the treatment of opioid and other addictions.13-15 Schenberg et al.16 looked retrospectively at 75 patients treated with ibogaine at an addictions clinic in Brazil. The patients, who abused crack, cocaine, heroin, cannabis, or alcohol, underwent anywhere from one to nine treatment sessions with the alkaloid. Subsequent results showed an overall abstinence rate of 61% at a median follow up of 5.5 months.16 In addition to formal studies, there are numerous observational and non-experimental accounts similarly corroborating the therapeutic properties of ibogaine.14

Ayahuasca is another plant derived psychedelic with renewed research focus. Traditionally consumed as a tea, ayahuasca initially gained interest when it was noted that both recreational and ceremonial use of the drug were associated with lower addiction rates in parts of Brazil17 and served a fundamental part of several addictions treatment programs in Peru.18 More locally, ayahuasca has been actively supported by Canadian physician and addictions specialist, Dr. Gabor Maté, who has led numerous therapeutic ayahuasca retreats with members of First Nations communities struggling with addictions issues.19 These retreats were found to result in statistically significant decreases in cocaine use, as well as improvements in multiple other measures of psychological health and quality of life.18

Current strategies for the treatment of addictions report poor success rates, with twelve step programs having minimal effect on alcohol dependence.20 Harm reduction strategies such as needle exchanges and supervised injection sites, however, have made great strides in improving the morbidity associated with IV drug use.21 Methadone maintenance programs and naltrexone take home kits have similarly made for safer drug use.22,23 Despite this, the individual and social consequences of drug addiction remain far-reaching. The economic, healthcare and law-enforcement costs of drug addiction have been estimated at $39.8 billion CAD per year.24 Furthermore, our current strategies do little to address the root cause of addiction resulting in an undeniable need to develop new strategies for combating drug addiction.

The factors preventing the further exploration of these substances include both political and financial considerations. In both Canada and the United States, regulatory measures remain a significant barrier. The majority of psychedelic substances require exemption under Section 56 of the Controlled Drugs and Substances Act,25 which historically has been a challenging and lengthy process. This is best demonstrated by past attempts to acquire exemption of ayahuasca use for religious purposes in Canada. In 2001, a request was made by the Céu de Montréal church
to allow the importation, possession and consumption of Daime tea (another term for ayahuasca) for ceremonial use. The application was deemed low risk and approval was initially recommended by Health Canada six years later. In 2011 however, this request was eventually denied by Federal Health Minister Leona AghaKaa. At this time, Dr. Maté was also threatened with being reprimanded should he continue his work with ayahuasca in people living with addiction. Likewise, ibogaine has undergone similar challenges when attempts have been made to formally investigate its anti-addictive properties, despite being currently unregulated in Canada. While a study for this purpose was approved in B.C., the process took years and researchers were subjected to limitations in study design which made results difficult to interpret. Similar limitations also apply to LSD, as approval for its study as a therapeutic agent in recent years has largely been restricted to its role in alleviating anxiety in a palliative care setting. There have been no further studies investigating its role in addiction treatment since the studies conducted in the 50’s and 60’s, presumably as a result of aforementioned difficulties. These strict regulatory measures not only deter the study of psychedelics in general, but also create barriers preventing researchers from obtaining the substances for study.

For researchers that overcome the hurdle of gaining government approval, additional challenges exist with obtaining funding. A large majority of researchers rely on funding from private sources, charitable organizations such as Multidisciplinary Association for Psychedelic Studies, various non-government organizations, or crowd-funding campaigns. It has also been argued that a lack of monetary incentive for studying these drugs is an additional contributing factor, given that they have been shown to be effective in only one or two doses, while other prescription drugs are taken on a long term basis.

The benefits of further research are not limited to the direct therapeutic effects of hallucinogens. Researching these compounds also has the potential to shed light on the biochemical etiology of addiction and other mental health issues. An example of this is the classic hallucinogen 4-iodo-2,5-dimethoxyphenylisopropylamine (DOI). DOI has been found to increase brain derived neurotrophic factor, the levels of which are inversely correlated with alcohol consumption. Studying these substances may also help elucidate the psychological factors at play in addiction, given the nature of the experiences described by those who have used psychedelics. This is supported by several studies that have shown hallucinogen use to have persisting effects on the brain in terms of beliefs, values and even personality. Research would also allow further insight into their therapeutic role in other mental health issues, as demonstrated by one study that showed reduced rates of mental illness and suicidality associated with psychedelic use and another that found promising results using 3,4-methylenedioxymethamphetamine (MDMA) for treatment of post-traumatic stress disorder in combination with psychotherapy.

This is not a proposition that psychedelic substances are a panacea, but rather an argument in support of fully exploring the potential role of psychedelics as adjuncts in the treatment of addictions and other mental illnesses. In doing so we may open the door to new therapies that have the possibility to assist patients in making meaningful and lasting improvements in their psychological health.

References

24. Thomas GR, Davis CG. Computing the Perceived Seriousness and Actual Costs of Substance Abuse in Canada: Analysis drawn from the 2004 Canadian Addiction Survey. 2006; Ottawa, ON: Canadian Centre on Substance Abuse.
31. Drug use in Canada: Analysis drawn from the 2004 Canadian Addiction Survey. 2006; Ottawa, ON: Canadian Centre on Substance Abuse.
Tackling social isolation and loneliness through community exercise programs for seniors

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Abstract

Social isolation is a growing problem among Canadian seniors, and along with loneliness, has been related to negative health effects and increased morbidity and mortality. The majority of senior recreation programs and the studies that surround them focus on physical benefits, while ignoring the effects of the programs on social isolation and loneliness. Furthermore, few community programs in Canada currently incorporate socialization sessions into exercise programs. This article attempts to highlight studies that focus on tackling the issue of social isolation and loneliness in traditional community senior exercise programs, and the potential role of sustained socialization-based exercise programs on improving seniors’ health.

The population of Canadian seniors (ages 65 years and older)¹ is projected to double in the next 25 years² and for the very first time, the number of seniors will surpass the number of children. As one ages, social networks decline such that over 30% of Canadian seniors are at a risk of becoming socially isolated³. Social isolation is defined as a quantifiable measure of a reduced social network (i.e. number and quality of social, family, and friend contacts).³ Social isolation is closely related to loneliness, which is a subjective measure of the negative feelings associated with a perceived lack of social network.³ Major risk factors for seniors’ social isolation and loneliness can be divided into five categories that include physical (e.g. hearing loss), psychological (e.g. depression), economic (e.g. retirement status), changes in work and family roles (e.g. loss of a loved one), and environmental (e.g. living alone).⁴ From a clinical perspective, social isolation and loneliness relates to negative effects on seniors’ psychosocial well-being and physical health. Loneliness has been associated with increased rates of depression, cognitive decline, impaired sleep, increased vascular resistance, increased systolic blood pressure, and altered immunity.⁵ In addition, many studies have also linked social isolation to an increase in premature mortality.⁶,⁷,⁸

In British Columbia, major cities offer recreation programs to allow the growing senior population to stay active. Benefits of community exercise programs on physical health and mortality in seniors have been studied extensively in literature. Unfortunately, many ignore the potential uses of these programs on mitigating social isolation and loneliness. As the effects of social isolation and loneliness are becoming more apparent in the senior population, this article attempts to highlight studies that focus on tackling the issue of social isolation and loneliness in traditional community senior exercise programs.

In Finland, a randomized controlled trial was conducted in seven daycare centers with 235 seniors (age 74 years or older) suffering from loneliness.⁹ Prior to randomization and based on their personal preference, participants chose either group exercise and discussion (n=92), therapeutic writing and group psychotherapy (n=48), or art activities (n=95). Each group was subsequently randomized 1:1 into control (usual community care) and intervention groups. Interventions took place over a three-month period and consisted of 12 sessions each. After two years, the survival rate of the three intervention groups (97%; 95% CI 91-99) was statistically significantly higher than the control group (90%; 95% CI 83-95) (p=0.042), but due to the small sample size, the 95% CI overlapped. In addition, the intervention group had greater improvements in subjective health (p=0.007), which is a strong predictor of survival, and decreased use of healthcare services (p=0.039). Subjective health is how individuals perceive their own health ranging from feeling “very unhealthy” to “healthy” on a four-point scale. This implies that programs of this nature may reverse deteriorating health as well as decreasing social isolation.

In 2014, researchers in Australia investigated the factors which motivate older people to engage in physical activity.⁵ Researchers created a community-based physical activity program and interviewed ten participants between the ages of 62 and 75 years old. While the program did not consider ‘socialization’ as a motivational component, research showed that ‘social interaction’ was mentioned by all participants as an important reason for their involvement. It allowed participants to create meaningful friendships and gain freedom from social isolation. Friendship and social interaction not only contributed to their original involvement in a given community program, but also helped maintain or reignite their interest. The data supported the notion of community-based exercise programs having a socialization component to help participants develop friendships and relieve social isolation.

To address this gap, Walk N’ Talk for Your Life (WTL) was developed in September 2014 by CJ. The WTL program was guided by input from over 200 older adults living in six low-income housing residences in Calgary, Alberta. Located in Kelowna, British Columbia. WTL is a student and community volunteer-run socialization, health education, and physical health program focused on alleviating loneliness and social isolation, as well as improving physical function among seniors. It was created based on feedback from community members, who requested a program that incorporates socializing, physical activity, and health education. Since its inception, over 300 seniors have participated in WTL programs held in eight separate community locations. WTL continues for its third year at one location, and funding has recently been obtained to carry the program on for three more years. Additionally, it has been adopted into ongoing weekly programming by the staff at another seniors’ residence. The program runs twice weekly for 12 weeks. Participants attend a thirty-minute
COMMENTARY

According to the study, there is a need to raise awareness about the effects of loneliness and social isolation on morbidity and mortality, and the potential role of sustained socialization–based exercise programs to combat these factors and improve seniors’ health.

References
I would tell you if I could: Language loss, depression, and the challenge of treating patients with aphasia

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Abstract
People with aphasia are prone to depression as a result of communication challenges associated with their language disorder. These same communication challenges greatly limit their ability to benefit from psychotherapy, one of the most recommended therapies for mental illnesses like depression. This commentary describes the unique cognitive interaction between aphasia and depression, and offers some evidence-based communication strategies, such as Supported Conversation for Adults (SCA) with Aphasia, that can help facilitate the therapeutic process for people with aphasia who are also experiencing depression.

Psychotherapy is one of the most efficacious treatments for depression and is based on the core idea that talking through problems can help change negative thoughts or change perspectives. But what if your ability to talk is impaired? Aphasia, a language disorder caused by damage to the brain, affects approximately 30% of people following a stroke event. Having aphasia is known to significantly increases the risk of depression. Unfortunately, people with aphasia are uniquely disadvantaged in their ability to access therapy for mental illness, due to their language impairment. The very thing that could help to alleviate the strain of mental illness—the ability to communicate—is the very thing that is impaired. Communication is both the casualty and the remedy.

There are approximately 100,000 Canadians living with aphasia, nearly twice as many as with Parkinson’s Disease. While most Canadians have likely heard of Parkinson’s, aphasia is not nearly as well known. This might be attributed to the wide variability of aphasia subtypes and etiologies. No two brains are the same; no two strokes.

Aphasia can disrupt any aspect of language processing including: speaking, comprehension, reading, or writing. The type of aphasia depends upon the location and severity of the brain injury. While other aspects of cognition might also be affected by the brain injury, aphasia—in and of itself—does not affect one’s intelligence. Aphasia is classified into two main categories: expressive and receptive. In expressive (non-fluent) aphasia, a person knows what they want to say, but struggles to produce spoken or written language, with a spectrum ranging from mild word-finding difficulty, to disjointed speech, to the inability to say any words at all. In receptive (fluent) aphasia, a person can still speak smoothly, but their language content may have little or no meaning and include an array of misplaced or nonsensical words. People with receptive aphasia are often unaware of their impairment, because their auditory comprehension is typically the most affected language domain.

What, then, unifies these two categories of aphasia? There are several areas in the left (or dominant) cerebral hemisphere, surrounding the lateral sulcus, that play a critical role in speech and language, including: Broca’s area, Wernicke’s area, the angular gyrus, and the auditory cortex. Language processing, however, is a dynamic system that is distributed throughout the entire brain. Language relies on all aspects of cognition including: memory, attention, encoding, activation, inhibition, and timing mechanisms. It is valuable, therefore, to consider the complex interplay between cognitive processing and mental health. Aphasia and depression are both brain-based disorders that place demands on the same system: a single neural network with finite capacity. While the brain is plastic and remarkable in its ability to rewire and compensate after injury, all resources have limits.

At least 30% of stroke survivors suffer from depression. Prevalence is much higher, up to 70% three-months post-stroke, when complicated with aphasia. While the prevalence tends to decrease over time (rates reduce to 62% at 12-months post-stroke), rates of major depression reportedly rise from 11% to 33% in a 12-month period. The type of aphasia also seems to be a factor, with expressive aphasia being the strongest predictor of depression.

It would be an oversimplification to say that aphasia causes depression. However, given the powerful relationship between communication and identity, it comes as little surprise that aphasia might open a door to depression. Symptoms of depression include persistent sadness, dependence, indecision regarding physical and cognitive difficulties, and—in extreme cases—suicidal thoughts. Aphasia, like depression, is largely an invisible impairment. We cannot see damage to the left inferior frontal gyrus (causing expressive aphasia) the way we can see a broken leg. When one meets a person in a wheelchair, one might think to hold the door open for them, but what about a person with aphasia? A language disorder is more difficult to identify, let alone accommodate for, especially when the general population knows little about it. People with aphasia are routinely confronted by impatient listeners, confused looks, and communication breakdowns. Social isolation can be a long-term result of aphasia, further diminishing mental health. Not only is day-to-day communication a challenge, so is accessing the medical system. Imagine a person in a wheelchair who needs to see a psychiatrist, but cannot enter the building due to the lack of ramps and elevators. An equivalent accessibility issue exists for people with aphasia. Not only is there reduced access to healthcare for people with communication disorders, but also lower satisfaction with the healthcare system and higher rates of medical errors.

With respect to treatment of depression in people with aphasia, careful assessment is the first step, but many standard assessments
for depression are inadequate because they rely on the client’s language ability to confirm signs and symptoms. Fortunately, tools have been developed to bridge this gap. The Stroke Aphasia Depression Questionnaire and the Aphasic Depression Rating Scale rely primarily on caregiver report and the Depression Intensity Scale Circles is a simple, graphic scale designed for individuals with communicative deficits following brain injury.23-25 These tools all demonstrate good validity and reliability as screens for depression in people with aphasia.18,21-25 Behavioural therapy is shown to benefit people with aphasia.26 Speech–language pathologists are in a unique position to educate other healthcare professionals about effective, aphasia-friendly communication techniques.27 Research demonstrates that training conversation partners in conversation strategies can help minimize the disability of aphasia.27 Implementing this training and raising awareness about its importance can dramatically increase communication opportunities for people with aphasia.

One specific conversation strategy, Supported Conversation for Adults with Aphasia (SCA), is based on the concept that people with aphasia “know more than they can say.”28,29 SCA trains conversation partners to facilitate conversation by writing down key words, using gestures, drawing pictures, verifying the message has been understood, and acknowledging the competence of the person with aphasia. As of 2015, Canadian Stroke Best Practices recommend using SCA when providing healthcare to people with aphasia.30

More generally, supported conversation aims to reduce barriers and enhance interaction. To do this, a clinician working with a person with aphasia can make some specific accommodations such as speaking in clear, short sentences at a relaxed pace, and allowing the patient extra time for language processing.27 If the patient is struggling to get their message out, ask yes or no questions to clarify. Always check that you have understood them and they have understood you. Be flexible with communication modalities, incorporating writing, drawing, and gesture. Minimize environmental distractions, such as unnecessary noise, and ensure the patient can see your face. Consent forms and other important written documents should be made available in simplified language and graphics. Lastly, remember to speak to the patient in an appropriate and respectful tone. Their language has been impaired, not their intelligence.

Aphasia need not be a barrier to psychotherapy. Given the high incidences of depression amongst this vulnerable population, we should strive to meet this need, offer evidence-based care, and employ recommended communication strategies. The more that health care professionals learn about aphasia and how best to support communication, the more effectively depression can be identified and treated.

References

Concussion and mental health: A concise review

Alvin Ip, MD, BKin

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Abstract

Mental health following concussion is a highly topical issue at present. This article reviews the epidemiology, pathophysiology, and management of mental health issues following concussion. Concussion is common: the annual prevalence rate is estimated to be 110 per 100,000 population in Canada, but may be significantly higher as concussions are underrecognized and underreported. There is a relationship between concussion and poor mental health; for example, repeated concussions may cause cumulative neuropsychological deficits. Athletes who play contact sports and individuals who possess the apolipoprotein E epsilon4 (APOE e4) genotype may be more susceptible to experiencing mental health issues secondary to concussion. Concussion causes injury to the brain through shear strain, and neuroinflammation from repeated concussions may cause neurodegenerative changes. The management of mental health issues following concussion consists of education and reassurance, prevention of additional injury, and treatment of neuropsychiatric symptoms.

E emerging research, athlete activism, and the Hollywood movie, Concussion, starring Will Smith, have shone a spotlight on the important topic of mental health following concussion. Concussion is a brain injury caused by a direct blow or impulsive force transmitted to the head that results in neurological impairment, which typically resolves spontaneously. This may or may not involve loss of consciousness and no abnormality is typically seen on standard neuroimaging studies. It is important to note that all concussions are mild traumatic brain injuries (TBIs), but not all mild TBIs are concussions—this is because concussions represent the less severe end of the mild TBI spectrum. Concussion is common, with the annual prevalence rate estimated to be 110 per 100,000 population in Canada. However, this number may be significantly higher as many concussions are unrecognized or unreported. The purpose of this paper is to review the epidemiology, pathophysiology, and management of mental health issues following concussion.

There is a relationship between concussion and poor mental health. A recent Canadian longitudinal cohort study published in February 2016 found that adults with concussion committed suicide at three times the population norm. A nationwide study from Denmark found a strong correlation between head injury and mental health issues; in participants with mild TBI, the risk of subsequent schizophrenia was increased by 64%, the risk of depression by 59%, the risk of bipolar disorder by 35%, and the risk of organic mental disorders by 238%. However, the interpretation of this data must take into consideration that while all concussions are mild TBIs, not all mild TBIs are concussions. Psychological symptoms, including irritability, depression, anxiety, and emotional lability, are commonly reported following concussion. Studies have shown that concussions have negative effects on reaction time, processing speed, attention, and memory as demonstrated through neuropsychological assessment. Furthermore, advanced neuroimaging techniques using functional and structural MRI have demonstrated the consistency of depressed mood following concussion with a limbic–frontal lobe model of depression. Emerging research has purported that repeated concussions may cause cumulative neuropsychological deficits and chronic traumatic encephalopathy (CTE), which will be discussed further in this article.

The multiple etiologies of concussion include falls (47%), motor vehicle accidents (34%), blunt force trauma (11%), violence (5%), and others. It is noteworthy to highlight that 50% of all concussions in children and youth between 8 to 19 years of age seen in the Emergency Department were related to sports and recreational activities. Concussions are not infrequent occurrences in contact sports, which include American football, ice hockey, soccer, boxing, and rugby. It has been estimated that the concussion risk of an athlete playing a contact sport is as high as 20% per season. Given that athletes face a high incidence of sports–related concussion and usually return to sports post–concussion, this population may be more susceptible to experiencing mental illness secondary to concussion. Indeed, it is National Football League football players, college football players, and amateur soccer players, in whom repeated concussions and their cumulative neuropsychological effects have been studied.

Concussion is caused by a rapid rotational acceleration of the brain. The leading hypothesis for the pathophysiology of concussion is a shear strain injury to neural tissue resulting in neuronal depolarization, local lactic acid accumulation, decreased cerebral blood flow, and cerebral glucose supply–demand mismatch. One possible mechanism for the development of mental illness post–concussion has been studied in CTE, a clinical entity presenting with cognitive impairment, Parkinsonism, and neuropsychiatric symptoms that include agitation, psychosis, personality changes, depression, and suicidality. Post–mortem pathologic studies in patients with CTE have shown cerebral atrophy, cavum septum pellucidum fenestrations, and tau–immunoreactive degeneration of the cerebral cortex. These neurodegenerative changes are believed to be caused by a neuroinflammatory response to head trauma, but more research is needed. Genetics may play a role as well, as the apolipoprotein E epsilon4 (APOE e4) genotype has been associated with the severity of traumatic encephalopathy.

The management of mental health issues following concussion will be discussed within three domains: education, prevention of additional injury, and treatment. An important responsibility of the physician is to educate and support the patient, which has been shown to improve symptoms after concussion. Given that over 50% of patients experience personality change, irritability, anxiety, and depression, the physician should reassure the patient that these neuropsychiatric symptoms are not unique, but part of the natural course following concussion. It is also important to note that most
patients will achieve improvement in their symptoms within three months, and physicians should advise and reassure patients of this.30 Furthermore, it is critical to prevent additional injury after concussion and thus unique consideration should be given to athletes who are at higher risk of re-injury.3 Prior to returning to competitive sport, the clinician should advise for a period of physical and cognitive rest and the completion of a consensus graduated return to play protocol (Table 1).1,2 The development of longer term psychological conditions, which include anxiety, depression, panic disorder, and acute stress disorder, may occur in a minority of patients following concussion.7,12,19 Research, although limited, has demonstrated that cognitive behavioural therapy, cognitive remediation, antidepressants, and anticonvulsants are helpful in treating the neuropsychiatric symptoms of mild TBI.31,32 Patients who continue to experience persistent symptoms ten days after concussion should be referred to a specialist in physical medicine and rehabilitation, sports medicine, or neurology.30

Given that millions of people are at risk for concussion and the potential for long-term neuropsychological sequelae, mental health following concussion is an important health topic that warrants greater attention. There exists a relationship between concussion and poor mental health, and repeated concussions may cause cumulative neuropsychological deficits. It has been shown that athletes who play contact sports and individuals who possess the APOE e4 genotype are more susceptible to experiencing mental health issues secondary to concussion. Concussion causes injury to the brain through shear strain, while neurodegenerative changes from repeated concussions may be caused by neuroinflammation. Following concussion, the main pillars of mental health management include education and reassurance, prevention of additional injury, and treatment of neuropsychiatric symptoms. It is important to advance our knowledge of concussion and mental health, educate the public, especially those at higher risk, and advocate for concussion prevention.

References
The lasting effects of childhood trauma on mental health in adulthood: Current knowledge and practical next steps for clinical practice

Stephanie Lake, MSc

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Childhood trauma broadly refers to exposures to traumatic events in childhood, such as being abused or neglected by a parent or guardian, surviving a natural disaster or an act of terrorism, or witnessing the loss of a loved one. While broadly referring to traumatic experiences at any point of childhood and adolescence (i.e., under 18 years of age), the onset of childhood trauma occurs in younger years (i.e., 0-9 years old) for many individuals who experience it. Specifically, complex childhood trauma, the focus of this paper, refers to the types of traumatic exposures that tend to be experienced together and cumulatively over the course of childhood, including physical abuse, sexual abuse, emotional/psychological abuse, physical and emotional neglect, and exposure to domestic violence. Approximately one in three Canadians has a history of experiencing at least one form of childhood trauma, with the most frequently reported trauma being exposure to domestic violence. As the subject of an emerging and quickly evolving field of research within neurosciences, social epidemiology, and medicine, we are beginning to understand the high prevalence of childhood trauma and its potentially detrimental effects.

The Early Childhood Experiences study and other epidemiological findings

In the late 1990s, the Adverse Childhood Experiences (ACE) study was implemented in San Diego, California to understand the potential physical and mental health problems arising decades after exposure to childhood trauma. This retrospective cohort study gathered information related to childhood exposures from over 17,000 adults, and collected patient information related to clinical problems and health behaviours. Largely due to the research that has emerged from the ACE study, it is becoming abundantly clear that the effects of childhood trauma manifest in many forms and persist long after childhood. In addition to a long list of physical health problems, various childhood traumas act as risk factors for a wide range of mental health problems. Carr and colleagues recently reviewed the literature to summarize the mental health outcomes associated with five major types of childhood trauma: physical abuse, sexual abuse, emotional abuse, and physical and emotional neglect. In this review, childhood physical, sexual, and emotional abuse as well as physical and/or emotional neglect were found to be associated with mood disorders including major depression, anxiety disorders, schizophrenia, eating disorders, substance abuse disorders, and various personality disorders. Physical and sexual abuse were also linked with post-traumatic stress disorder, and sexual abuse was linked with bipolar disorder. Other types of childhood trauma not reviewed by Carr and colleagues, including witnessing domestic violence, have also been linked with many of the above outcomes. As suggested by the significant overlap between outcomes associated with the distinct trauma types, many survivors of childhood trauma report suffering multiple traumas throughout their childhood. For example, Afifi and colleagues recently analyzed data from a representative sample of Canadians and found that almost one-quarter reported two of three types of childhood abuse (physical, sexual, or witnessing intimate partner violence), and 8% had experienced all three. There is strong consensus within the literature of a dose-response relationship between childhood trauma and mental illness, such that the odds of developing an above-listed condition increase with the number of traumatic incidents experienced in childhood.

Neurobiological factors

Although epidemiologic studies describe a clear association between childhood trauma and mental health, neurobiological research provides critical insight into the underlying biopsychosocial pathways that lend a plausible explanation to these epidemiologic findings. The body’s stress regulating pathways may be disrupted when repeatedly exposed to sustained traumatic stress, including various forms of childhood abuse or neglect. As these stress exposures coincide with brain development, these disruptions may alter various endocrine pathways that can shape brain development, including memory storage and retrieval, social cognition, emotional attachment, emotional regulation, and coping skills.

Social factors

Not all those who are exposed to trauma in childhood will suffer from deteriorating mental health. Social epidemiological and psychological research has demonstrated that the trajectory of mental health may depend on various social influences among survivors of childhood trauma. For example, a strong social support network tends to improve psychological well-being among adult survivors of childhood trauma. Conversely, exposure to other social stressors including poverty, low social support, social marginalization, discrimination, parental mental illness, and/or substance abuse may interact to promote poor mental health among survivors.

Detecting childhood trauma among adults in medical practice

Given the high prevalence and widespread health implications of childhood trauma, identifying a history of trauma among patients is necessary for clinicians to successfully aid in preventing or treating health problems that can develop in adulthood. Unlike many physical health problems, there are no clear and definite signs of prior childhood trauma, but some behavioural and clinical symptoms that may be indicative of a traumatic history include dissociation, anxiety, depression, suicidal ideation, chronic pain, and substance abuse or addiction. If a clinician suspects a patient may have been exposed to a form of trauma in their childhood, they may refer the patient to...
a specialist for further assessment, or they may administer a formal assessment through a validated questionnaire, such as the Childhood Trauma Questionnaire. In a study assessing clinician practices of screening for childhood trauma among adult patients, Weinreb et al. found that less than one-third of surveyed primary care physicians reported “usually” or “always” screening for childhood trauma. Common barriers to screening included a lack of knowledge about childhood trauma, a lack of confidence in screening, and a perception that screening was not part of their role as a primary care physician. These barriers demonstrate that clinician education, related to the prevalence and potential impacts of childhood trauma and appropriate screening and response methods, may be the first step in responding appropriately to the potential health problems associated with childhood trauma. In the study by Weinreb et al., over one-third of physicians had not received any formal training in screening adult patients for childhood trauma. Becoming skilled in identifying childhood trauma is especially pertinent for clinicians who are specializing in mental health. One way of addressing this educational barrier could be by building this training into medical school curriculums and continuing education training programs. Furthermore, the development of clinical guidelines describing when and who to screen for childhood trauma may clarify the role physicians should play in addressing childhood trauma.

**Trauma-informed care**

Aside from simply learning to screen patients, optimizing the physician–patient relationship with survivors of childhood trauma is essential to addressing their health needs. Trauma-informed care is a promising method that has been successfully taught through continuing education. This patient-centered method of communication and care is guided by the clinician’s understanding of the potential health effects of trauma, as well as the range of situational perceptions common to trauma survivors, particularly within a medical setting. The aim of trauma-informed care is to promote a culture of empathy, sensitivity, safety, and acceptance in order to facilitate engagement, trust, and retention in preventative medical care for trauma survivors.

In conclusion, a large proportion of the Canadian population has been affected by childhood trauma. The medical system must adapt to the emerging research demonstrating compelling evidence for immense health implications that survivors of childhood trauma may face in adulthood. While the development of methods specifically tailored to trauma survivors is a promising approach to minimizing the health burden for trauma survivors, governing and managing bodies within the health care and educational systems should explore large-scale changes that work to bridge the gap that remains.

**References**

Burnout and mental illness among Canadian physicians

Alan Rheaume, BSc(Hons) 1

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When ancient Mayans experienced mental illnesses, such as depression and anxiety, the community united in a sacred ritual called the limpia to purify the mind and body. 1 Folk healers combined medicinal practices with public ceremonies to heal the affected individual while strengthening the spiritual fabric of the entire community. 1 The social ritual vindicated sufferers of stigma by emphasizing the interconnectedness of the healing process—physical and mental, individual and collective.

In Canada, burnout and mental illness have become an increasing problem among physicians. 2 The phenomenon of burnout was first documented by American psychologist Herbert Freudenberger in 1974, who described burnout as a state of physical and mental exhaustion in response to chronic stress in the workplace. 3, 5 While there remains no consensus on a definition for burnout, three common features of burnout syndrome are: 1) emotional exhaustion; 2) depersonalization and alienation toward work–related activities and people; and 3) reduced workplace performance or sense of accomplishment. 3, 5 While concrete data are lacking for Canadian physicians, rates of burnout in the United States approach half of all doctors. 6

The insidious effects of burnout can slowly develop through years of caregiver stress, psychological trauma, and long working hours. 2 Initial signs of burnout, such as irritability and dissatisfaction, can spiral into interpersonal conflict, inconsistent performance, erratic behaviour, irrational judgment, social isolation, and absenteeism. 7 Coping with the stress of professional duties outside of the workplace may cause strain to adversely impact a physician's personal life. For example, many physicians answer their work email at home, while some get called to work outside of their scheduled practice and on–call hours. Over half of Canadian physicians feel their personal lives have been negatively impacted by their professions. 8 A physician with burnout may experience decreased personal satisfaction at home and impaired capacity to engage in restorative lifestyle behaviours. Conversely, decreased life satisfaction can erode personal and professional relationships at home and work, leading to further exhaustion and alienation. 9

The consequences of physician burnout impact all levels of health care and society. 1 Over 50% of physicians report that high stress, sleep deprivation, and mental exhaustion negatively affect their patient care. 10 Burnout can impair cognitive functioning and clinical reasoning, leading to medical error. 10-12 For instance, residents who met the criteria for depression made 6.2 times more medication errors than non–depressed peers. 12 The broader economic cost of burnout on early retirement and reduced clinical hours in Canada is estimated at $185.2 million and $27.9 million per year, respectively. 11 Yet, the greatest potential economic burdens of burnout and years lived with disability remain under–reported: mental illness, substance use, and suicide.

Burnout and work–related stress precipitate and exacerbate mental illness and substance use. Roughly two–thirds of Canadian physicians perceive their workload as too demanding. 1 In a comprehensive health study of 3,213 Canadian physicians, one in four reported mental health problems in the past month that made handling their workload difficult. 13 This study measured the prevalence of depression over one year as 20% among male physicians and 29% among female physicians. These statistics may underestimate the actual prevalence, however, due to the stigma associated with self–reporting mental health issues. 15

One outcome of untreated physician burnout and mental illness is suicide—the most common cause of death for doctors under 35 years of age. 16 Despite having lower overall mortality, in part due to exceptional physical health, Canadian physicians have a significantly higher risk of death by suicide. 9, 17, 18 Relative to the general population, the risk of suicide among physicians is 1.1 to 3.4 times higher for males, and 2.5 to 5.7 times higher for females. 19 Among physicians who committed suicide, the most common psychiatric illnesses are mood disorders and substance abuse. 20 Given the health–seeking tendencies of Canadian physicians for physical ailments, why are mental illnesses often untreated?

Personal values, professional obligations, and societal standards deter physicians from recognizing or addressing mental health problems. 29 A physician's health may be considered an indicator of medical competence among patients and colleagues, especially when health concerns affect work performance. 21 Effective clinical reasoning, medical competence, and safe patient care require sufficient physical and mental functioning. 26 If physicians experience mental health problems, their colleagues, patients, and society may begin to doubt the physician's ability to provide a high standard of care. Pressure to perform can lead physicians to avoid their medical problems altogether—a sentiment easily rationalized by the prevailing ethical obligation to "put patients first". 2

Physicians may also fear that disclosing mental illness will affect their professional standing. Frequently, licensing bodies ask about history of mental health problems in the process of applying for or renewing medical licenses. 22 Moreover, medical boards of hospitals and clinics often inquire about previous mental health treatment among applicants. 23 Whether or not these inquiries directly influence medical licensing or employment decisions is unclear, but the actual or perceived discrimination toward mental illness creates a culture of secrecy around mental health.

Stigma and discrimination against mental health issues prevent many Canadians from seeking treatment. 25 One in five Canadians live with mental illness, yet more than 60% of people with mental health problems do not seek help due to barriers such as stigma. 24 Among doctors, stigma surrounding mental illness is particularly apparent. The culture of medicine reinforces the myth that doctors are invincible, high–achieving martyrs who should never show signs of weakness or sickness. 21, 25, 26 The majority of physicians living with mental illness never seek professional help—even if they know they need it. 2 Only 2% of Canadian physicians with depression seek treatment for their illness. 27 In response to rising physician stress, medical organizations have
started to prioritize physician health in their policies and advocacy efforts. In 2010, the Canadian Medical Association (CMA) released a mental health strategy outlining a comprehensive approach to combat rising stress and health issues among physicians.  

Most recently, the Royal College of Physicians and Surgeons of Canada (RCPSC) declared physician health and well-being a core professional competency in the 2015 CanMEDS Framework. This framework emphasizes a shared responsibility to promote a culture that is inclusive and supportive toward physicians in need.

Several programs and initiatives aimed at helping physicians have been introduced in recent years. The CMA’s provincial divisions offer physician health programs in each of the ten provinces to provide assistance to physicians and their families. In British Columbia, the Physician Health Program operates a free 24-hour hotline that provides confidential health services, counselling, and education for physicians experiencing personal or professional problems.

As a follow-up to the CanMEDS Framework, the RCPSC published a physician health handbook in 2009 that provides physicians with practical information and health resources. These efforts reflect the contemporary shift in attitude that has brought issues of physician health to the forefront of discussions in medicine.

Emerging research suggests several strategies that doctors can use to manage stress. A 2014 Cochrane Review of stress reduction interventions for healthcare workers reported that Cognitive Behavioural Therapy, meditation, and mindfulness practices are all helpful approaches to reducing burnout.

In addition, having control over work hours and schedule can alleviate stress and increase career satisfaction. Other lifestyle interventions, such as exercise, adequate sleep, and proper nutrition, can positively benefit physician health. Further research is needed to identify effective interventions for physician health programs and preventative care.

Despite recent research and efforts to reverse the trend of physician burnout and mental illness, many future challenges exist. Many of the stressors physicians face in their training and practice are inherent to the demanding medical profession. Within this competitive field, physicians are hesitant to talk about mental health issues, making research and grassroots advocacy difficult. Physicians entering the workforce in the next decade must learn to cope with additional stress from new advancements in technology and the complex health issues of an aging Canadian population. The health care system must adapt to meet these challenges while addressing the critical issues of physician burnout, mental illness, and suicide.

The communal Mayan limpia treated mental illness by healing the community. If you are a physician experiencing excessive stress or burnout in your workplace or personal life, and would like support or assistance from a trained confidential physician or counsellor, consider calling the BC Physician Health Program Hotline toll-free at 1-800-663-6729. For the full list of provincial contacts, visit the CMA website at: http://www.cma.ca/En/Pages/provincial-physician-health-programs.aspx

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From the ability to detect rare germ-line variants which predispose multiple sclerosis to the generation of highly efficacious cell-based treatments for cancer, high-throughput sequencing techniques and genetic engineering have afforded considerable improvements to patient care. In other avenues, proteomic network analysis is enabling us for the first time to understand the evolution of cell lineages while coupling ultrasound with robotic engineering resolves the dynamic architecture of organs during laparoscopic surgery. The aim of this UBCMJ issue to explore the challenges and inform on the interplay between technology and medicine as these fields align to keep our society healthy. Furthermore, we hope that this issue will help identify areas of healthcare that are in critical need of support from recent technological advances.

To encourage and recognize high quality writing, we will be presenting the UBCMJ Distinguished Writing Award (with a $250 honorarium) to the strongest article submitted in the Fall 2016 and Spring 2017 issues.

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